Published in final edited form as:

Int J Cardiol. 2018 October 15; 269: 207–212. doi:10.1016/j.ijcard.2018.06.087.

Preventable Delays to Intravenous Furosemide Administration in the Emergency Department Prolong Hospitalization for Patients with Acute Heart Failure

Michael J. Ward, MD, PhD, MBA^{*,1,2,3}, Sean P. Collins, MD, MSc^{1,2,3}, Dandan Liu, PhD^{1,4}, and Craig M. Froehle, PhD^{1,5}

¹This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

²Department of Emergency Medicine, Vanderbilt University Medical Center

³Tennessee Valley VA Healthcare System

⁴Department of Biostatistics, Vanderbilt University School of Medicine

⁵Carl H. Lindner College of Business, Department of Operations, Business Analytics and Information Systems, University of Cincinnati, and Department of Emergency Medicine, University of Cincinnati

Abstract

Background: We sought to examine whether factors impacting the time to emergency department (ED) administration of intravenous (IV) furosemide were associated with the duration of hospital admission for patients with acute heart failure (AHF).

Methods and Results: We conducted a single-center, retrospective analysis of patients presenting to the ED and admitted between January 1, 2007 and December 31, 2014 who received a dose of IV furosemide. A Cox proportional hazards model was used to examine the likelihood that a patient would be discharged home alive, adjusting for patient demographics, AHF severity (low, moderate, high), laboratory result timing, and known AHF confounders. We identified 695 patients who met study criteria with 430 (61.9%) in the low-severity group. In the overall model, every 60-minute delay in IV furosemide administration was associated with an 8% lower chance of successful discharge home relative to someone who received early furosemide (aHR 0.93, 95%CI 0.87, 0.98, $p=0.012$). Subgroup analysis suggests this association was most impactful in low-acuity patients. Our adjusted analysis suggests delaying furosemide administration until after serum creatinine results resulted in a 41% lower chance of successful discharge home relative to

*Corresponding Author: Michael J. Ward, MD, PhD, MBA, 1313 21st Ave, Nashville, TN, USA 37232, Phone: 615-936-8379; michael.j.ward@vanderbilt.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Declarations of interest: none

Disclosures: None

someone who had furosemide administered prior to creatinine results (aHR 1.41, 95%CI 1.07, 1.84).

Conclusions: AHF patients, particularly those with lower severity, may benefit from rapid administration of IV furosemide in the ED. This suggests that a key determinant of hospital visit duration in this low-risk cohort is decongestion, which occurs sooner when IV therapy is begun early in the ED stay regardless of serum creatinine.

Keywords

Translational Studies; Cardiopulmonary Resuscitation and Emergency Cardiac Care; Heart Failure; Quality and Outcomes; Treatment

INTRODUCTION

Heart failure is a chronic, costly, debilitating, and deadly disease with an annual mortality rate of 10% that increases in prevalence as individuals age.¹ The emergency department (ED) plays an important role in acute heart failure (AHF) management and resource use. In the U.S., there are an estimated one million ED visits annually for AHF,^{2, 3} and over 80% of heart failure patients continue to be admitted by ED providers.² Of the \$39 billion in annual U.S. expenditures for heart failure care,¹ the single largest proportion is due to hospitalization,^{4, 5} costing the U.S. \$11 billion annually⁶ and affecting 5–6 million people.^{3, 7} While the ED plays a vital role in the decision to admit AHF patients, little research has explored the role of ED care on downstream clinical and operational outcomes for patients with AHF.

Prior research suggests a relationship between early initiation of intravenous (IV) AHF therapy in the ED with beneficial clinical and operational outcomes.^{8–10} ED administration of IV vasoactive agents reduced in-hospital mortality within the first 48 hours of admission.⁸ ED treatment delays with IV diuretics were modestly associated with increased in-hospital mortality.⁹ Similarly, delays to first IV AHF treatment (loop diuretics, inotropes, or vasodilators) in ED patients over 65 years of age hospitalized with AHF were associated with higher in-hospital mortality and longer inpatient length of stay, but were not associated with 30-day outcomes.¹⁰ Finally, among 1,291 patients treated with IV furosemide after presenting to the ED, those who were treated within 60 minutes of arrival to the ED had significantly reduced odds (0.39, 95%CI 0.2, 0.76) of in-hospital mortality.¹¹

However, these prior studies have limitations that make their applicability regarding timing of furosemide administration to ED patients difficult to interpret, such as: 1) selecting only patients eligible for Medicare,¹⁰ and those in practice settings that have disproportionately longer lengths of stay;¹¹ 2) analyzing patients who receive a combination of IV furosemide and IV vasoactives; and 3) evaluating in-hospital mortality as the primary endpoint.

Considering the aforementioned limitations, our objective was to evaluate the relationship between the timing of ED administration of IV furosemide and likelihood of successful discharge home from the hospital in a broad setting of AHF presenting to the ED for emergency care.

MATERIALS AND METHODS

We conducted a retrospective analysis of ED patients presenting with AHF to Vanderbilt University Medical Center (VUMC), an academic, tertiary care, level 1 trauma center in Nashville, TN, USA. There is a heart failure program at VUMC providing surgical and non-surgical care to patients with heart failure. This study was approved by the VUMC Institutional Review Board.

Data were extracted from the VUMC Enterprise Data Warehouse (EDW). The variables extracted included patient demographics, clinical variables regarding AHF treatment, and operational data about timing and duration of care in the ED and inpatient settings. Considering that all patient mortality data may not be reported in the VUMC EDW, we also searched the Social Security Death Index for patient mortality. Inclusion and exclusion criteria followed existing clinical research standards for studies of AHF patients in the ED.¹² We wanted to include a patient population not only felt to have AHF in the ED, but also had a diagnosis of AHF once they were admitted. We felt this was important in an analysis investigating timing of medication administration, because if either the ED or inpatient teams did not diagnose AHF, both the timing of treatment and the patient's hospital length of stay could be affected.

Patients were included in this study if presented to the VUMC ED between January 1, 2007 and December 31, 2014. Patients had to have a primary, secondary, or tertiary ED diagnosis combined with a primary, secondary, or tertiary inpatient diagnosis of heart failure defined by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) classification codes (428.x, 428.xx, 402.x1, 404.x1, and 404.x3). Patients had to have at least one dose of IV furosemide administered while in the ED, although other diuretics could also be administered (e.g., bumetanide) during their ED stay. Patients were required to have a b-type natriuretic peptide (BNP) level drawn while in the ED, enhancing the likelihood that AHF was in the differential diagnosis while enabling a secondary analysis of the association between treatment administration and timing of BNP results. However, we did not require a specific level as this may be confounded by renal function¹³ or body mass index.¹⁴

If patients did not initially present to the ED or were transferred from another facility, they were excluded from the analysis. Initial care at another facility may introduce confounders into our results due to variability in practice patterns at other institutions. Moreover, prolonged transfer times may also diminish treatment effects. Of note, we did not exclude patients if they presented with a subsequent AHF exacerbation. We reasoned that the prior episode had resolved and re-presentation was distinct.

Analysis

Our objective was to examine the relationship of timing of IV furosemide administration timing with the likelihood of successful discharge home. Since length of stay in healthcare is subject to the competing risk of death (i.e., a shorter length of stay is not always better), the analysis had to simultaneously consider patient mortality. While some patients may not die, aggressive efforts to treat the patient may cease if the patient has advanced directives

indicating that no additional treatments should take place, or that the patient and/or family has decided to go to hospice for end-of-life care. To account for the competing risk of expected or actual death, we modeled the cause-specific hazard of discharge home alive using Cox proportional hazard model.¹⁵

Applied to our study on IV furosemide administration timing, the primary outcome was the timing of successful discharge home alive for an admitted AHF patient. As we used a cox proportional hazard model, we defined the time period of hospitalization as the duration from the hospital admission order until the hospital discharge was ordered by the treating physician. We defined the censoring event included in our survival analysis as any of the following: 1) death; 2) hospice care; and 3) transfer to another institution. We included transfer because complete records may not be available after the patient leaves the hospital. In addition, since we did not use multiple groups to compare their relative hazards, we used the timing of IV furosemide administration for all included patients.

The following potential confounders were included as covariates: patient age, sex, and insurance status (Medicare, Medicaid, Private, Other). To account for severity of illness, we adapted a measure of AHF severity from Fonarow et al.,¹⁶ which used hospitalization data from the Acute Decompensated Heart Failure National Registry (ADHERE), as the count of the following: lowest systolic blood pressure <115 mm Hg, blood urea nitrogen level ≥43 mg/dL, plasma creatinine ≥2.75 mg/dL, and elevated troponin. Although troponin was not one of the identified variables, we included it as prior work has identified sensitive troponin as a prognostic indicator of AHF prognosis.¹⁷ As no formally accepted decision aid exists to risk stratify AHF patients, we used the count of these predictors as an indicator of low (zero factors), intermediate (one factor), and high (two or more factors) severity of AHF. We also included emergency severity index (ESI) triage level as the initial assessment by the ED staff of the overall acuity of the patient at triage, intensive care unit (ICU) admission from the ED, admission to a cardiology service from the ED, arrival by emergency medical services, cumulative IV administered dose of furosemide in the ED, order-to-administration time interval of furosemide before/after the BNP result, and, finally, order-to-administration time interval of furosemide before/after creatinine result. For the laboratory results, we reasoned that some emergency clinicians may wait to administer furosemide until either of these tests returned results so we included indicator variables of both BNP and creatinine testing. Subgroup analyses for AHF severity were planned as severity was reasoned to influence the timing of furosemide administration. The proportional hazards assumption was checked for each variable based on scaled Schoenfeld residuals.¹⁸

RESULTS

There were 695 patients between January 1, 2007 and December 31, 2014 who directly presented to the ED at VUMC, had both an ED and inpatient diagnosis of AHF, and had a BNP drawn in the ED. The identification of the study population can be seen in Figure 1 and patient demographics can be seen in Table 1. Approximately one-third of subjects in the initial database of 1,043 were excluded for discordance between the ED and inpatient diagnoses of heart failure, approximately another third for not receiving an IV dose of furosemide, and the remainder of the original dataset (55, 5.3%) were excluded for either

missing data such as adjusting variables or outcomes of interest. Of the final subjects included in the study, nearly two-thirds corresponded with the lowest severity, one quarter were moderate-severity (one severity marker), and the remainder were high-severity (two or more severity indicators). The majority of included patients were white males, with a median age of 66 years. Length of stay in the ED for admitted AHF patients similarly decreased in duration as AHF severity increased. The median inpatient length of stay from ED disposition through hospital discharge was between 3 and 4 days. Finally, 30-day mortality increased as AHF severity increased.

Examining the timing of care provided in the ED (Table 1), 82% of patients received only one IV medication (i.e., furosemide) during their ED stay with the remainder of patients receiving two or more IV medications. The arrival-to-bed placement interval for this population was between 10 and 12 minutes. On average, most patients received an initial IV treatment with furosemide under three hours and this duration decreased as AHF severity increased. Patients with AHF were also more likely to receive a higher cumulative dose of IV furosemide as their severity increased. Nearly two-thirds of patients received IV furosemide after BNP results and almost 80% of AHF patients in the ED received IV furosemide after creatinine results were available.

In order to better understand the timing of IV furosemide administration, we calculated descriptive statistics by the variable of interest (Supplemental Table). Patients with AHF had significantly shorter arrival-to-furosemide durations if they arrived to the ED by EMS, were eventually admitted to a cardiology team or to the ICU, received two or more IV medications while in the ED, or received IV furosemide before BNP or creatinine laboratory testing results were available. However, administration times were similar by severity level (Figure 2).

In our Cox regression models, the proportional hazards assumption was met. In the overall model (Table 2, first column), the arrival-to-furosemide duration variable was significantly related to hospital length of stay ($p=0.012$) with an adjusted hazard ratio (aHR) of 0.93 (95% CI 0.92, 0.93). Every 60-minute delay of IV furosemide administration was associated with an 8% lower chance of being discharged to home during their hospital stay. Administration of IV furosemide prior to creatinine laboratory results was the only variable that remained significant in: 1) the overall, 2) interaction, and 3) low-severity models.

To examine whether the relationship between timing of furosemide administration and likelihood of hospital discharge may be dependent upon AHF severity independently, we developed another model with an interaction term for severity with the low-severity group as the referent. In this model, only the arrival-to-furosemide duration in the low-severity group was significant, while the other two groups were not. Sub-group analyses by severity levels (Table 2, 2nd - 4th columns) supported this finding with a significant relationship between arrival-to-furosemide in the low-severity AHF group ($p=0.005$). We created one final model examining whether there was an interaction of furosemide dose with timing of administration on hospital length of stay, and there was no significant relationship found.

DISCUSSION

We examined the timing of IV furosemide administration with hospital length of stay in a cohort of 695 ED patients with AHF. We intentionally restricted our patient population in order to identify subjects with AHF who received IV furosemide in the ED prior to admission. Further, this study includes a patient population not only felt to have AHF in the ED, but diagnosed by the inpatient setting with a diagnosis of AHF limiting the heterogeneity of the patient population for evaluating treatment effects. Our study has three important findings. First, we found that in the overall cohort of AHF patients presenting to and admitted from the ED, there was a significant association of IV furosemide administration timing with successful discharge home. Second, this finding appears to be driven by those patients with the lowest AHF severity. Third, when furosemide administration was delayed until after laboratories returned there was also a significant association with successful discharge home. This suggests clinicians may be waiting for laboratory results prior to administration of IV furosemide, resulting in a significant treatment delay and prolonging hospitalization. Our findings add to the current literature^{9–11} by demonstrating an association between ED process factors, timing of furosemide administration, and successful discharge. Further, our results identify the importance of early treatment and decongestion even in those patients with a low severity of acute illness.

The ED is a complex environment and many factors may influence the timing of IV furosemide administration in the ED. Patient AHF severity (but not triage severity), how the patient arrives to the ED (e.g., EMS), speed of the triage process, and whether the cause of the current illness is readily apparent can all affect the timing of furosemide administration. Even when seen quickly by a clinician, laboratory results may further influence the timing of medication administration. We found that most AHF patients presenting to the ED in this study did not receive IV furosemide until after creatinine and BNP results were available. While obtaining a BNP level is a class I recommendation from the ACCF/AHA guidelines to help identify AHF in undifferentiated patients with shortness of breath,¹⁹ its use prior to IV furosemide administration may have limited utility when the diagnosis is readily apparent base on physical exam, lung ultrasound or chest radiograph.²⁰ Further, in the DOSE trial, which included patients with moderate renal dysfunction, there was no clinically significant change in renal function when comparing high- versus low-dose furosemide.²¹ In our study population, we found that patients were 41% less likely to be discharged home when IV furosemide was held until after serum creatinine results. Therefore, in light of this work, delaying treatment of patients with AHF, particularly those with suspected volume overload has questionable value. This research not only reinforces that treatment of congestion with IV loop diuretics remains a pillar of ED management of AHF,²² but that the timing of administration has downstream implications for AHF patients admitted to the hospital. While optimal dosing of IV furosemide is still not well understood, empiric treatment of suspected AHF volume overload with IV furosemide may have meaningful consequences to the patient and broader healthcare system.

We attempted to understand the downstream influence of ED furosemide administration on hospital discharge. We found that each hour delay in IV administration of furosemide was associated with a nearly 8% lower chance of being discharged to home. The lack of an

interaction effect with severity and treatment timing combined with our sub-group analyses further support our findings that the overall effect is likely driven by the low-severity AHF population, where a delay in ED diagnosis and treatment may have the greatest impact. Given potential confounders, such as simultaneous treatment, factors influencing hospital discharge, and potential underlying etiologies of the patient's AHF exacerbation, the small effect size is also not surprising. However, this effect is also consistent with our hypothesis: during an initial presentation to the ED, timing of diagnostics and treatment in the ED and admission location can influence the downstream consequences of ED activities. Similar to when a patient is started on an inaccurate antibiotic dose and admitted to the hospital, inappropriate dosing can be maintained throughout the hospitalization.²³

We suspect that the moderate- and high-severity AHF groups were not affected for two reasons. First, the groups with higher severity received IV furosemide more rapidly, potentially diminishing the effect of IV furosemide. This is likely due to a combination of the AHF presentation being more readily apparent, and the severity of symptoms compelling the physician to administer therapy prior to diagnostic testing results. Second, higher admission severity is associated with prolonged hospital length of stay, costs, and adverse events, particularly for patients with AHF.²⁴ Nonetheless, the low-severity group comprised nearly two-thirds of the study population and averaged nearly three-hours to received IV furosemide. This presents a substantial opportunity for further study and possible practice changing implications.

Notably, triage severity was not significantly associated with the primary outcome. This may be because all patients were triaged to one of two categories creating little difference among the groups. In addition, the emergency severity index scale applies to all patients, not just AHF, and not only assigns severity of illness, but the number of resources as well.

Currently, timing of IV furosemide administration is not formally recognized as a priority for ED patients presenting with AHF, and if we improve systems of care for this patient population, this may have substantial cost and safety implications. Every additional day of hospitalization is associated with a higher risk of preventable adverse events from drug reactions, infection, and pressure ulcers.²⁵ Thus, efforts that can be initiated in the ED to reduce inpatient length of stay may have not only cost implications, but safety reasons as well.

LIMITATIONS

Our study reinforces the potential benefits of rapid IV furosemide administration in the ED for patients with AHF, but limitations exist. First, this was a single-center study with a moderate sample size, which limited our ability to examine how the administration of additional medications affected outcomes. Second, the single-center nature of this study limits the generalizability of the findings due to potentially unique practice patterns at the study site and clinical practice heterogeneity, such as the outpatient medication regimen, ED treatments not captured in this study, likelihood to admit, or the dosing of IV furosemide. Third, the retrospective nature of this data collection prevented the reliable identification of symptom onset time. This is limiting because patients may have different thresholds for

presenting to the ED and may wait until their condition is more severe, as has been seen in other acute emergencies such as stroke and myocardial infarction.^{26–29} Furthermore, discharging a patient with AHF home following an inpatient stay is complex and may be affected by myriad factors not routinely captured such as socioeconomic status, clinical condition, health literacy, and resources available at home including family support. Fourth, approximately one-third of the study population was excluded for discordance between the ED and inpatient diagnosis. The ED functions in an environment of uncertainty in which a patient's illness may not be clear and their diagnostic capabilities are limited. In the acute setting, diagnostic uncertainty exists, which may delay diagnosis of AHF. Prior research of AHF patients in Europe found a smaller degree of discordance. However, the AHF population in this study was based in the U.S. and included nearly one-third of patients being admitted through the medical/cardiac intensive care units. In addition, this European study used chart review rather than diagnostic codes to evaluate diagnoses as occurred in our study. Emergency physicians may be more reluctant to empirically diagnose a patient with AHF and could explain why so many patients received IV furosemide after laboratory result availability. We excluded patients who did not receive their initial IV dose of furosemide in the ED. We felt these patients could confound our analysis because either they were admitted due to another active comorbidity with AHF severity so mild they could forgo IV furosemide, or they may have been more of a diagnostic dilemma whose diagnosis was not clear until after admission. Next, laboratory result availability did not ensure that the emergency physician was actually aware of the results, merely that the results could be viewed. However, the electronic health record did have an indicator for lab availability which may reduce the time between availability and physician review. Finally, this analysis does not account for therapies received prior to arrival in the ED, particularly IV furosemide. However, a 10% sample of charts found that no patient who called 911 received IV furosemide prior to ED arrival.

CONCLUSION

We found that patients presenting to the ED with AHF who had delayed IV administration of furosemide were less likely to be successfully discharged home. This finding was likely driven by the low-severity population of ED AHF patients and clinicians waiting for serum creatinine results. Our findings suggest that although relatively brief, care provided in the ED may have important downstream implications for patients admitted with AHF. Further research is needed to better evaluate how robust this effect is in other populations, the optimal dosing of IV furosemide, and other factors that contribute to delays to administration of furosemide.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

None

Sources of Funding: Dr. Ward is supported by NIH K23 HL127130. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

REFERENCES

1. Neubauer S. The failing heart--an engine out of fuel. *N Engl J Med* 2007;356:1140–51. [PubMed: 17360992]
2. Storrow AB, Jenkins CA, Self WH, Alexander PT, Barrett TW, Han JH, McNaughton CD, Heavrin BS, Gheorghiade M and Collins SP. The burden of acute heart failure on U.S. emergency departments. *JACC Heart Fail* 2014;2:269–77. [PubMed: 24952694]
3. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Judd SE, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Mackey RH, Magid DJ, Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER, 3rd, Moy CS, Mussolino ME, Neumar RW, Nichol G, Pandey DK, Paynter NP, Reeves MJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Wong ND, Woo D, Turner MB, American Heart Association Statistics C and Stroke Statistics S. Heart disease and stroke statistics—2014 update: a report from the American Heart Association. *Circulation*. 2014;129:e28–e292. [PubMed: 24352519]
4. Heidenreich PA, Trogdon JG, Khavjou OA, Butler J, Dracup K, Ezekowitz MD, Finkelstein EA, Hong Y, Johnston SC, Khera A, Lloyd-Jones DM, Nelson SA, Nichol G, Orenstein D, Wilson PW, Woo YJ, American Heart Association Advocacy Coordinating C, Stroke C, Council on Cardiovascular R, Intervention, Council on Clinical C, Council on E, Prevention, Council on A, Thrombosis, Vascular B, Council on C, Critical C, Perioperative, Resuscitation, Council on Cardiovascular N, Council on the Kidney in Cardiovascular D, Council on Cardiovascular S, Anesthesia, Interdisciplinary Council on Quality of C and Outcomes R. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. *Circulation*. 2011;123:933–44. [PubMed: 21262990]
5. Weintraub NL, Collins SP, Pang PS, Levy PD, Anderson AS, Arslanian-Engoren C, Gibling WB, McCord JK, Parshall MB, Francis GS, Gheorghiade M, American Heart Association Council on Clinical C, Council on Cardiopulmonary CCP and Resuscitation. Acute heart failure syndromes: emergency department presentation, treatment, and disposition: current approaches and future aims: a scientific statement from the American Heart Association. *Circulation*. 2010;122:1975–96. [PubMed: 20937981]
6. Pfunter AW, LM. Steiner C. Costs for Hospital Stays in the United States, 2011, HCUP Statistical Brief #168. 2013.
7. Bui AL, Horwich TB and Fonarow GC. Epidemiology and risk profile of heart failure. *Nature reviews Cardiology*. 2011;8:30–41. [PubMed: 21060326]
8. Peacock WF, Emerman C, Costanzo MR, Diercks DB, Lopatin M and Fonarow GC. Early vasoactive drugs improve heart failure outcomes. *Congestive heart failure (Greenwich, Conn)*. 2009;15:256–64.
9. Maisel AS, Peacock WF, McMullin N, Jessie R, Fonarow GC, Wynne J and Mills RM. Timing of immunoreactive B-type natriuretic peptide levels and treatment delay in acute decompensated heart failure: an ADHERE (Acute Decompensated Heart Failure National Registry) analysis. *Journal of the American College of Cardiology*. 2008;52:534–40. [PubMed: 18687247]
10. Wong YW, Fonarow GC, Mi X, Peacock WF, Mills RM, Curtis LH, Qualls LG and Hernandez AF. Early intravenous heart failure therapy and outcomes among older patients hospitalized for acute decompensated heart failure: findings from the Acute Decompensated Heart Failure Registry Emergency Module (ADHERE-EM). *Am Heart J* 2013;166:349–56. [PubMed: 23895819]
11. Matsue Y, Damman K, Voors AA, Kagiya N, Yamaguchi T, Kuroda S, Okumura T, Kida K, Mizuno A, Oishi S, Inuzuka Y, Akiyama E, Matsukawa R, Kato K, Suzuki S, Naruke T, Yoshioka K, Miyoshi T, Baba Y, Yamamoto M, Murai K, Mizutani K, Yoshida K and Kitai T. Time-to-Furosemide Treatment and Mortality in Patients Hospitalized With Acute Heart Failure. *Journal of the American College of Cardiology*. 2017;69:3042–3051. [PubMed: 28641794]

12. Kaji AH, Schriger D and Green S. Looking through the retrospectroscope: reducing bias in emergency medicine chart review studies. *Ann Emerg Med* 2014;64:292–8. [PubMed: 24746846]
13. McCullough PA, Duc P, Omland T, McCord J, Nowak RM, Hollander JE, Herrmann HC, Steg PG, Westheim A, Knudsen CW, Storrow AB, Abraham WT, Lamba S, Wu AH, Perez A, Clopton P, Krishnaswamy P, Kazanegra R, Maisel AS and Breathing Not Properly Multinational Study I. B-type natriuretic peptide and renal function in the diagnosis of heart failure: an analysis from the Breathing Not Properly Multinational Study. *Am J Kidney Dis* 2003;41:571–9. [PubMed: 12612980]
14. Christenson RH, Azzazy HM, Duh SH, Maynard S, Seliger SL and Defilippi CR. Impact of increased body mass index on accuracy of B-type natriuretic peptide (BNP) and N-terminal proBNP for diagnosis of decompensated heart failure and prediction of all-cause mortality. *Clin Chem* 2010;56:633–41. [PubMed: 20167699]
15. Brock GN, Barnes C, Ramirez JA and Myers J. How to handle mortality when investigating length of hospital stay and time to clinical stability. *BMC medical research methodology*. 2011;11:144. [PubMed: 22029846]
16. Fonarow GC, Adams KF, Jr., Abraham WT, Yancy CW, Boscardin WJ, Adhere Scientific Advisory Committee SG and Investigators. Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. *JAMA*. 2005;293:572–80. [PubMed: 15687312]
17. Arenja N, Reichlin T, Drexler B, Oshima S, Denhaerynck K, Haaf P, Potocki M, Breidthardt T, Noveanu M, Stelzig C, Heinisch C, Twerenbold R, Reiter M, Socrates T and Mueller C. Sensitive cardiac troponin in the diagnosis and risk stratification of acute heart failure. *J Intern Med* 2012;271:598–607. [PubMed: 21988283]
18. Grambsch PM and Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika*. 1994;81:515–526.
19. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW and Westlake C. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation*. 2017;136:e137–e161. [PubMed: 28455343]
20. Martindale JL, Wakai A, Collins SP, Levy PD, Diercks D, Hiestand BC, Fermann GJ, deSouza I and Sinert R. Diagnosing Acute Heart Failure in the Emergency Department: A Systematic Review and Meta-analysis. *Acad Emerg Med* 2016;23:223–42. [PubMed: 26910112]
21. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, LeWinter MM, Deswal A, Rouleau JL, Ofili EO, Anstrom KJ, Hernandez AF, McNulty SE, Velazquez EJ, Kfoury AG, Chen HH, Givertz MM, Semigran MJ, Bart BA, Mascette AM, Braunwald E, O'Connor CM and Network NHFCR. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med* 2011;364:797–805. [PubMed: 21366472]
22. Collins SP, Storrow AB, Levy PD, Albert N, Butler J, Ezekowitz JA, Felker GM, Fermann GJ, Fonarow GC, Givertz MM, Hiestand B, Hollander JE, Lanfear DE, Pang PS, Peacock WF, Sawyer DB, Teerlink JR and Lenihan DJ. Early management of patients with acute heart failure: state of the art and future directions--a consensus document from the SAEM/HFSA acute heart failure working group. *Acad Emerg Med* 2015;22:94–112. [PubMed: 25423908]
23. Fuller BM, Mohr N, Skrupky L, Mueller K and McCammon C. Emergency Department vancomycin use: dosing practices and associated outcomes. *J Emerg Med* 2013;44:910–8. [PubMed: 23260465]
24. Naessens JM, Campbell CR, Shah N, Berg B, Lefante JJ, Williams AR and Culbertson R. Effect of illness severity and comorbidity on patient safety and adverse events. *Am J Med Qual* 2012;27:48–57. [PubMed: 22031176]
25. Hauck K and Zhao X. How dangerous is a day in hospital? A model of adverse events and length of stay for medical inpatients. *Med Care*. 2011;49:1068–75. [PubMed: 21945976]
26. Lacy CR, Suh DC, Bueno M and Kostis JB. Delay in presentation and evaluation for acute stroke: Stroke Time Registry for Outcomes Knowledge and Epidemiology (S.T.R.O.K.E.). *Stroke*. 2001;32:63–9. [PubMed: 11136916]

27. Kothari R, Jauch E, Broderick J, Brott T, Sauerbeck L, Khoury J and Liu T. Acute stroke: delays to presentation and emergency department evaluation. *Ann Emerg Med* 1999;33:3–8. [PubMed: 9867880]
28. Gharacholou SM, Alexander KP, Chen AY, Wang TY, Melloni C, Gibler WB, Pollack CV, Jr., Ohman EM, Peterson ED and Roe MT. Implications and reasons for the lack of use of reperfusion therapy in patients with ST-segment elevation myocardial infarction: findings from the CRUSADE initiative. *Am Heart J* 2010;159:757–63. [PubMed: 20435183]
29. McDermott K, Maynard C, Trivedi R, Lowy E and Fihn S. Factors associated with presenting >12 hours after symptom onset of acute myocardial infarction among Veteran men. *BMC Cardiovasc Disord.* 2012;12:82. [PubMed: 23020779]

Highlights:

- Among acute heart failure (AHF) patients presenting to and admitted from the ED, there was a significant association of IV furosemide administration timing with successful discharge home.
- Our findings appear to be driven by those patients with the lowest AHF severity.
- When furosemide administration was delayed until after laboratories returned there was also a significant association with successful discharge home.
- Our study identifies the importance of early treatment and decongestion even in those patients with a low severity of acute illness.

Figure 1.
Flow chart of patients who met inclusion/exclusion criteria for the study population.

Figure 2.
Timing of furosemide administration by heart failure severity. All times are in minutes.

Table 1.

Demographics and treatment timing of ED heart failure patients included in the study, by severity. All times are in minutes. *Note:* BNP, brain natriuretic peptide; EMS, emergency medical services; ICU, intensive care unit; IQR, interquartile range.

	Low Severity (N=430)	Moderate Severity (N=174)	High Severity (N=91)	Combined (N=695)
Age, y, median (IQR)	66 (54, 76)	66 (56, 74)	68 (59, 79)	66 (56, 76)
Sex, Female, N (%)	234 (54)	69 (40)	36 (40)	339 (49)
Race, N (%)				
White	183 (58)	82 (63)	46 (66)	311 (60)
Black	132 (42)	46 (35)	24 (34)	202 (39)
Other	2 (1)	2 (2)	0 (0)	4 (1)
Insurance, N (%)				
Medicare	156 (36)	72 (41)	50 (55)	278 (40)
Private	193 (45)	68 (39)	32 (35)	293 (42)
Medicaid	45 (10)	19 (11)	3 (3)	67 (10)
Other/Uninsured	36 (8)	15 (9)	6 (7)	57 (8)
Arrival by EMS, N (%)	103 (24)	55 (32)	33 (36)	191 (27)
Cardiology Admitting Team, N (%)	311 (72)	139 (80)	78 (86)	528 (76)
ICU Admission, N (%)	21 (5)	13 (7)	14 (15)	48 (7)
Cumulative Furosemide Administered in ED, median (IQR), mg	40 (40, 80)	45 (40, 80)	80 (40, 80)	40 (40, 80)
BNP Value, median (IQR), pg/mL	877 (445, 1,613)	1,111 (568, 1,973)	2,073 (921, 3,271)	1,009 (484, 1,897)
ED Length of Stay, median (IQR), min	511 (381, 722)	468 (362, 704)	429 (314, 720)	487 (369, 712)
Inpatient Length of Stay, median (IQR), days	3 (2,5)	4 (2, 6)	4 (3, 8)	4 (2, 5)
30 Day Mortality, N (%)	12 (2.8)	8 (4.6)	14 (15.4)	34 (4.9)
<i>Treatment Timing</i>				
ED Arrival to Bed Placement	11 (4, 27)	12 (3, 29)	10 (1,18)	11 (3, 25)
Arrival to IV Administration, median (IQR), min				
IV Furosemide (N=430)	170 (113, 244)	161 (108, 219)	155 (98,251)	166 (110, 241)
IV Antibiotic (N=29)	164 (119, 274)	171 (109, 275)	157 (104, 262)	164 (118, 272)
IV Vasodilator (N=21)	92 (43, 234)	83 (60, 121)	113 (58, 328)	90 (52, 160)
Timing of Laboratory Results				
Arrival-to-BNP Result Interval, median (IQR), min	148 (115, 192)	139 (110, 189)	150 (107, 197)	146 (112, 192)

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

	Low Severity (N=430)	Moderate Severity (N=174)	High Severity (N=91)	Combined (N=695)
Arrival-to-Creatinine Result Interval, median (IQR), min	89 (70, 130)	95 (69, 134)	95 (75, 120)	91 (70, 129)

Table 2.

Results for the overall model and by severity (low, moderate, high).

Variable	Model (Hazard Ratio, 95%CI, p value)			
	Overall	Sub-Group Analyses		
		Low-Severity	Moderate-Severity	High-Severity
Arrival to IV Furosemide	0.93 (0.92 – 0.93) P=0.012	0.9 (0.83 – 0.97) P=0.005	0.89 (0.77 – 1.04) P=0.143	1.06(0.89–1.26) p=0.517
HF Severity				
Low		<i>Reference</i>		
Moderate	0.72 (0.59 – 0.88) P=0.001	N/A	N/A	N/A
High	0.53 (0.4 – 0.7) P=<0.001	N/A	N/A	N/A
IV Furosemide Admin. Before BNP Result	0.99 (0.79 – 1.25) P=0.948	0.89 (0.67 – 1.18) P=0.403	1.24 (0.75 – 2.03) P=0.402	1.11 (0.5 – 2.46) P=0.795
IV Furosemide Admin. Before Creatinine	1.41 (1.07 – 1.84) P=0.013	1.69 (1.21 – 2.36) P=0.002	1.49 (0.83 – 2.68) P=0.186	0.56 (0.24 – 1.32) P=0.188
Primary Financial Class				
Medicare		<i>Reference</i>		
Private	0.87 (0.72 – 1.05) P=0.152	0.82 (0.65 – 1.04) P=0.1	0.78 (0.52 – 1.2) P=0.26	1.39 (0.7 – 2.78) P=0.349
Medicaid	1.1 (0.8 – 1.51) P=0.572	1.27 (0.86 – 1.87) P=0.238	0.7 (0.36 – 1.36) P=0.293	0.92 (0.09 – 9.53) P=0.946
Other/None	0.89 (0.63 – 1.27) P=0.525	1.04 (0.69 – 1.58) P=0.855	0.57 (0.24 – 1.38) P=0.214	0.48 (0.11 – 2.12) P=0.333
Race				
White		<i>Reference</i>		
Black	1.1 (0.89 – 1.34) P=0.387	1.07 (0.83 – 1.39) P=0.592	1.11 (0.71 – 1.74) P=0.656	0.84 (0.37 – 1.9) P=0.673
Other	0.51 (0.18 – 2.34) P=0.193	0.23 (1.23 – 2.23) P=3.23	1.74 (0.38 – 8.02) P=0.475	1.09 (0.42 – 2.84) P=0.859
Initial Triage Acuity	1.18 (0.93 – 1.49) P=0.165	1.19 (0.89 – 1.59) P=0.25	0.98 (0.56 – 1.71) P=0.942	1.43 (0.6 – 3.38) P=0.421
Arrival by EMS	0.68 (0.56 – 0.84) P=<0.001	0.64 (0.49 – 0.84) P=0.001	0.77 (0.51 – 1.17) P=0.218	0.9 (0.46 – 1.78) P=0.77
Patient Sex (Ref=Female)	1 (0.84 – 1.19) P=0.993	0.97 (0.77 – 1.21) P=0.762	1.18 (0.8 – 1.76) P=0.404	1.12 (0.62 – 2.02) P=0.709
Patient Age	0.99 (0.99 – 1) P=0.062	1 (0.99 – 1.01) P=0.874	0.97 (0.96 – 0.99) P=0.002	0.99 (0.96 – 1.01) P=0.351
Admitted to a Cardiology Team	1.27 (1.04 – 1.56) P=0.021	1.36 (1.07 – 1.72) P=0.013	0.85 (0.53 – 1.37) P=0.516	1.47 (0.55 – 3.91) P=0.437
Admission to the ICU	0.69 (0.47 – 1) P=0.052	0.54 (0.31 – 0.95) P=0.031	0.68 (0.32 – 1.46) P=0.326	0.93 (0.35 – 2.47) P=0.88
Cumulative Furosemide Dose	1 (1 – 1) P=0.473	1 (0.99 – 1) P=0.457	0.99 (0.99 – 1) P=0.132	1 (0.99 – 1.01) P=0.989