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Is Time of the Essence? The Impact of Time of Hospital Presentation in Acute Heart Failure: Insights from ASCEND-HF

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Abstract

Background—Time of hospital presentation has been shown to impact outcomes among patients hospitalized with many conditions. However, the association between time of presentation and patient characteristics, management, and clinical outcomes among patients hospitalized with acute heart failure (AHF) has not been well-characterized.

Methods—A *post-hoc* analysis was performed of the ASCEND-HF trial, which enrolled 7141 patients hospitalized for AHF. Patients were divided based on when they presented to the hospital, with regular hours defined as 9am-5pm Monday-Friday and off-hours defined as 5pm-9am Monday-Friday and weekends. Clinical characteristics and outcomes were compared by time of presentation.

Results—Overall, 3298 (46%) patients presented during off-hours. Off-hours patients were more likely to have orthopnea (80% vs. 74%) and rales (56% vs. 49%) compared to regular hours patients. Off-hours patients were more likely to receive IV nitroglycerin (18% vs. 11%) and IV loop diuretics (92% vs. 86%) as initial therapy and reported greater dyspnea relief at 24 hours (odds ratio [OR] 1.14, 95% confidence interval [CI] 1.04–1.24, p = 0.01), compared to regular hours patients. After adjustment, off-hours presentation was associated with significantly lower 30-day mortality (OR 0.74, 95% CI 0.57–0.96, p = 0.03) and 180-day mortality (HR 0.82, 95% CI 0.72–0.94, p = 0.01) but similar 30-day rehospitalization (p = 0.40).

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Conclusion—In this AHF trial, patients admitted during off-hours exhibited a distinct clinical profile, experienced greater dyspnea relief, and had lower post-discharge mortality compared with regular hours patients. These findings have implications for future AHF trials.

Keywords

Heart Failure; Presentation; ASCEND-HF

Introduction

The time of presentation to the hospital may influence healthcare quality and patient outcomes. Within cardiology, this concept is best recognized in the context of ST elevation myocardial infarction (STEMI), where patients admitted during off-hours may experience longer door to balloon times and higher in-hospital mortality than those admitted during regular business hours [1]. Worse outcomes for those admitted during off-hours has also been observed for patients admitted for primary arrhythmia, ruptured aortic aneurysm, acute pulmonary embolism, and non-cardiac conditions [2, 3]. However, despite heart failure (HF) being a leading cause of hospitalization annually in the United States [4], data regarding the influence of time of presentation on patient profile are limited and the impact of time of admission on initial management and outcomes is uncertain. It has been hypothesized that early therapy and rapid decongestion may lead to better long-term outcomes in the acute HF (AHF) population [5–7]. A recent prospective observational study demonstrated early intravenous diuretic administration was associated with lower in-hospital mortality [8]. Given differences in hospital staffing and operation, time of day may impact the rapidity of decongestion and subsequent long-term outcomes. Moreover, as prior AHF clinical trials have targeted earlier enrollment after initial presentation (i.e., within 16–24 hours) [9, 10], understanding the clinical profiles and outcomes of patients according to timing of presentation is relevant to trial design and conduct. A recent study demonstrated that patients presenting to the hospital for AHF at nights were more symptomatic than those presenting during daytime, but had lower 180-day mortality [11], suggesting important differences in AHF patients presenting during regular and off-hours.

As the largest AHF trial conducted to date, the global Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial database offers an opportunity to systematically describe the relationship between time of hospital presentation, clinical profile, inpatient management, and outcomes among patients admitted with AHF.

Methods

Overview

The study design [12] and primary results [13] of the ASCEND-HF trial have been previously reported. Briefly, ASCEND-HF was an international, prospective, multicenter, randomized, double-blind, placebo-controlled trial examining the short- and long-term efficacy and safety of nesiritide, a recombinant natriuretic peptide. The trial enrolled 7141 patients hospitalized for AHF with a reduced or preserved ejection fraction as evidenced by dyspnea with minimal activity or at rest, ≥1 accompanying sign, and ≥1 objective measure.

Patients were randomized to treatment (i.e., study baseline) with nesiritide or placebo, in addition to standard therapy, within 24 hours of the first intravenous therapy for HF. Exclusion criteria included a high likelihood to be discharged from the hospital in ≤24 hours or life expectancy of <6 months due to a comorbid condition. The ASCEND-HF trial was conducted in accordance with the Declaration of Helsinki, the protocol was independently approved by the institutional review board or ethics committee at each participating center, and written informed consent was obtained from all patients.

Study Definitions and Endpoints

For this *post-hoc* analysis, patients were divided into two groups based on time of presentation to the hospital (defined as when they registered at the hospital), regular hours defined as 9am-5pm Monday-Friday and off-hours defined as 5pm-9am Monday-Friday and weekends. These cutoffs were chosen to reflect the typical hours of outpatient clinics, regular business activity, and clinical trial enrollment, and mirror similar analyses in the STEMI population [1, 3, 14]. As a sensitivity analysis, outcome analyses were repeated with regular hours defined as 7am-7pm Monday-Friday and off-hours defined as 7pm-7am M-F and weekends [11].

Dyspnea relief was measured using a self-reported 7-point Likert scale (i.e. markedly worse from baseline = −3, moderately worse = −2, minimally worse = −1, no change = 0, minimally better = 1, moderately better = 2, and markedly better = 3). For the present analysis, the primary outcome was the composite of hospitalization for HF or death within 30 days. In addition, the present analysis also examined several secondary outcomes, including 30-day hospitalization and all-cause mortality and 180-day all-cause mortality. An independent and blinded adjudication committee determined the cause of all hospitalizations and deaths occurring within 30 days. Hospitalization for HF was defined as admission for worsening signs or symptoms of HF resulting in the new administration of intravenous therapies, mechanical or surgical intervention, or provision of ultrafiltration, hemofiltration, or dialysis specifically for the management of persistent or worsening HF.

Statistical Analysis

Baseline characteristics, including demographics, medical history, lab values, and medication use, were described for those presenting during regular hours vs. off-hours using median (25^{th}, 75^{th} percentile) for continuous variables and frequency (%) for categorical variables. Comparisons between time of presentation groups were performed using two-sided Wilcoxon rank sum test for continuous variables and chi-square test for categorical variables and the threshold for statistical significance was a p-value <0.05. Similar approaches were employed to investigate the associations between time of presentation inpatient therapies and 24-hour markers of congestion. Ordinal logistic regression models were used to assess the association of time of presentation to dyspnea relief at 24 hours. The proportional odds assumption was verified. Unadjusted analyses controlled for geographic region, and adjusted analyses controlled also for site enrollment volume in addition to 17 pre-specified covariates either previously utilized in ASCEND-HF mortality and dyspnea models, or added *a priori* per clinical judgment [15, 16]. The method of multiple imputations was utilized to impute missing data for the adjustment variables, assuming that the data was

missing at random. Ten multiply-imputed datasets were used, and in general, the rate of missingness for all variables was less than 10%.

Logistic regression models were used to assess the association between time of presentation and 30-day mortality and re-hospitalization, 30-day mortality, 30-day re-hospitalization. Cox regression models were used to assess the association between time of presentation and 180-day mortality. Unadjusted analyses for 30- and 180-day outcomes controlled for geographic region. Adjusted analyses controlled for the variables described previously [15, 16]. A sensitivity analysis was then performed to examine how the association between time of presentation and outcomes changed if off-hours was defined as 7pm-7am Monday-Friday and weekends, while regular hours patients were those presenting from 7am-7pm Monday-Friday. Generalized linear regression models were used to assess the association between time of presentation and hospital length of stay (defined as the number of days from presentation to discharge). We use Akaike information criteria to compare models fit assuming Gaussian, inverse Gaussian, and gamma distributions. The final models assumed an inverse Gaussian distribution with a log link function. Similar models included a two-way interaction between region and time of presentation to assess the potentially modifying effect of region on the association between time of presentation and length of stay. Statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC). Two-tailed $p<0.05$ was considered statistically significant.

Results

Characteristics of Groups by Time of Presentation

Overall, 3298 (46%) patients presented during off-hours. Patients who presented during off-hours were more likely to be female, self-report as non-white, and have a smoking history compared with regular hours patients (Table 1). The median LVEF was similar between the two groups and background and discharge guideline-directed medical therapy was distributed evenly with the exception that regular hours patients were more likely to be prescribed mineralocorticoid receptor antagonists. Baseline laboratory values including natriuretic peptide levels were similar between the two groups. Median times from presentation to randomization were 18 hours and 15 hours for regular hours and off-hours patients, respectively ($p=0.039$). There was no difference in treatment assignment. Patients presenting during off-hours were more likely to utilize emergency services for transportation to the hospital whereas regular hours patients were more likely to self-present. The number of patients presenting to the hospital was highest on Monday, with decreasing numbers throughout the rest of the week (Supplementary Table 1). Patients enrolled in North America, Latin America, and Western Europe presented more frequently during off-hours, whereas regular hours patients were more common among patients enrolled in Central Europe and Asia Pacific (Supplementary Figure 1).

Inpatient Management and Decongestion

Patients presenting during off-hours were more likely to have dyspnea at rest, orthopnea, and rales, but less likely to have peripheral edema (Table 1). Off-hours patients were more likely to receive loop diuretics and IV nitroglycerin prior to randomization, but there was no

between group difference in the number of patients receiving diuretics from presentation to 24 hours after randomization (Table 2). Patients presenting during off-hours reported significantly greater dyspnea relief at 24 hours, even after adjustment for baseline characteristics and medications, time from presentation to randomization, and treatment assignment (odds ratio [OR] 1.14, 95% confidence interval [CI] 1.04–1.24) (Table 3). When the definition of regular hours was modified to 7am-7pm Monday-Friday and off-hours was defined as 7pm-7am Monday-Friday and weekends, off-hours patients were found to still have significantly more dyspnea relief at 24 hours (odds ratio [OR] 1.18, 95% confidence interval [CI] 1.07–1.30) (Table 4) after adjustment for potential confounders. Patients in the off-hours group had significantly shorter hospitalizations (mean of 7.18 days versus 8.04 days) than those admitted during regular hours, even after adjustment for covariates (OR 0.93, 95% CI 0.89–0.95) (Supplementary Table 2). A two-way interaction analysis demonstrated that the association of time of presentation and length of hospitalization was not modified by geographic region (p=0.60 after adjustment) (Supplementary Table 3).

Association Between Time of Presentation and Outcomes

Patients admitted during off-hours were at lower risk for 30-day mortality after adjustment for potential confounders (hazard ratio [HR] 0.75, 95% CI 0.57–0.96, p=0.03) (Table 3). Overall, 30-day readmission rates were similar between the two groups and there was no difference between the groups in the composite endpoint of mortality and rehospitalization. Off-hour patients were at significantly decreased risk of 180-day mortality compared with regular hour patients after adjustment (HR 0.83, 95% CI 0.72–0.94, p=0.01) (Table 3, Figure 1). When a sensitivity analysis was performed to change the definitions of regular hours to 7am-7pm Monday-Friday and off-hours to 7pm-7am Monday-Friday and weekends, the difference in 30- and 180-day mortality between off-hours and regular hours patients was not statistically significant after adjustment (p=0.39 for 30-day mortality, p=0.29 for 180-day mortality) (Table 4). On sensitivity analysis, off-hours and regular hours patients had similar rates of 30-day rehospitalization and the composite endpoint of 30-day mortality and rehospitalization.

Discussion

In this large international trial of patients hospitalized for AHF, clinical characteristics varied based on time of hospital presentation. Notably, patients presenting during off-hours had more symptoms related to pulmonary congestion and were less likely to have peripheral edema. Compared with patients admitted during regular hours, off-hours patients were more likely to receive loop diuretics and nitroglycerin as part of initial therapy and reported more dyspnea relief 24 hours after randomization. There was no difference between groups in the composite of 30-day mortality and rehospitalization. However, off-hours patients had significantly lower 30- and 180-day mortality, even after adjustment for potential confounders.

Clinical Characteristics and Signs and Symptoms of Congestion

In this study, off-hour patients were more likely to exhibit signs and symptoms of pulmonary congestion (i.e. rales, orthopnea, dyspnea at rest, pulmonary edema on chest x-ray), whereas

patients admitted during regular hours were more likely to have signs of systemic congestion (i.e. peripheral edema). Despite reporting more signs and symptoms of pulmonary congestion at baseline, off-hour patients had lower long-term mortality rates, suggesting a potential paradox between presenting symptoms and outcomes. This differs from a prior analysis of ASCEND-HF that found resting dyspnea correlated to higher 30-day mortality [16], calling for more investigation into the prognostic significance of dyspnea on presentation. However, other studies have demonstrated that patients who present with elevated blood pressures are more likely to exhibit signs and symptoms of pulmonary congestion and paradoxically have better long-term outcomes [17, 18]. It is hypothesized that the ability to acutely increase blood pressure is a marker of greater cardiac reserve and that this reserve is the pathophysiologic basis of these patients having better long-term survival. In the present analysis, off-hours and regular hours patients had similar blood pressures yet demonstrated a dissociation between symptoms of congestion and long-term outcomes. The mechanisms and markers of this dissociation are not fully understood and are in need of further investigation.

Inpatient Treatment and Long-Term Outcomes

Despite presenting during off-hours, patients admitted overnight and on weekends were more likely to receive IV furosemide and nitroglycerin from presentation to randomization and were more likely to experience dyspnea relief at 24 hours post-randomization. This is in contrast to the STEMI population, where door-to-balloon times and overall survival is impacted by time of presentation [1, 3]. While time of day has been shown to affect the ability to assemble a multidisciplinary team to care for STEMI patients, this analysis does not demonstrate a meaningful difference in ability to administer decongestive therapy for AHF based on time of day.

Off-hours patients received slightly more diuretics and significantly more IV nitroglycerin between presentation and randomization and experienced increased dyspnea relief at 24 hours, as well as lower rates of 30- and 180-day mortality. Previous studies have demonstrated the importance of early decongestion in the clinical management of AHF [5, 19]. Early dyspnea relief has been shown to correlate with lower long-term event rates [20, 21], although this finding is controversial [22]. A recent prospective observational study found that early intravenous diuretic administration for AHF was associated with a lower risk of in-hospital mortality, strengthening this hypothesis [8]. In our study, the fact that off-hours and regular hours patients had clinically similar markers of decongestion (eg. UOP, body weight change at 24 hours) suggests that dyspnea relief is influenced by factors beyond volume removal [23]. This corresponds with a prior analysis of ASCEND-HF that demonstrated patients with early dyspnea relief had lower 30-day mortality or rehospitalization (compared to patients with little minimal or no dyspnea relief), although the risk of 30-day mortality alone was not significantly different after adjustment [15]. In that analysis, dyspnea relief could not be fully explained by age, renal function, or natriuretic peptides. Given these data, dyspnea relief appears to be an important prognostic indicator in AHF patients, although further research is required to explain the mechanisms of dyspnea relief.

Our results are similar to those of a recent analysis of Serelaxin, Recombinant Human Relaxin-2, for Treatment of Acute Heart Failure (RELAX-AHF), in which nighttime patients had lower risk of 180-day mortality that was statistically significant after multivariable adjustment [11]. However, in the present analysis, sensitivity analyses with modified group definitions exactly matching those used by the RELAX-AHF investigators (off-hours defined as 7pm-7am Monday-Friday and weekends), failed to demonstrate statistically significant differences in outcomes, with similar risk of 30- and 180-day mortality among off-hours and regular hours patients. While these varying results between the present primary and sensitivity analyses could represent true clinical differences driven by the reassigned subset of patients, sensitivity analysis results may also be a consequence of inadequate statistical power (i.e., 33% decrease in number of off-hours patients from the original analysis to sensitivity analysis), or multiplicity of testing. Nonetheless, the discrepant findings between primary and sensitivity analyses highlight challenges in studying time of presentation and underscore the importance of defining off-hours. The optimal definition of off-hours in AHF remains unclear and further investigation is warranted.

Clinical Trial Implications

The present analysis has several implications for the design of future AHF trials. To date, despite numerous clinical trials, there remain no available agents definitively proven to improve post-discharge outcomes. It has been proposed that the heterogeneity of the AHF study population, and/or the study design and execution are important reasons for the persistent lack of a positive clinical trial. For example, recent research has identified several important aspects of trial design, including region [24–26] and enrollment volume [27] that independently predict patient outcomes, and conceivably, could impact the ability of a trial to accurately assess the safety and efficacy of an investigational therapy.

The present analysis suggests that considering time of patient presentation to the hospital is another important domain to be considered in the design of AHF trials. The finding that time of presentation independently predicts post-discharge mortality may impact study power calculations for long-term outcomes. In addition, there is a trend among recent AHF trials to minimize the time from hospital presentation to randomization in efforts to potentially maximize chances of improving dyspnea, or to rapidly abort end-organ injury in hopes of improving long-term outcomes [9, 28]. Although patients in ASCEND-HF could be randomized up to 24 hours after first intravenous HF therapy, if future trials mandate enrollment very early (i.e., few hours) after presentation, our results suggest that dedicating substantial trial staff and resources for off-hours enrollment may be offset by lower post-discharge event rate among off-hours patients. Furthermore, increased dyspnea relief in off-hours patients may hinder the ability of an investigational therapy to show a dyspnea benefit over standard care. These considerations may influence investigators to focus on trial enrollment during regular hours, allowing cost savings while potentially capturing patients with a more modifiable short-term clinical course.

Limitations

There are several limitations of the data inherent to exploratory analyses. Firstly, this analysis is limited to the prespecified inclusion criteria of the original ASCEND-HF trial, limiting its generalizability. Many of the results and practices may be specific to the centers that enrolled in ASCEND-HF, limiting applicability to many real world heart failure patients. Secondly, many baseline characteristics were gathered at time of randomization, which was on average 18 and 15 hours after time of initial presentation for regular and off-hours patients, respectively. Interim clinical improvements and treatments between time of presentation and time of enrollment could have a substantial impact on the baseline data collected. Moreover, the gap naturally excluded patients with very early mortality (i.e., death before consent could be obtained) and patients with extremely rapid resolution of all congestive signs and symptoms Thirdly, it is subject to the intrinsic biases secondary to *post-hoc* analyses, including residual confounding. Fourthly, some of the measures reported are subjective, particularly data on dyspnea relief, which lacks a universally agreed upon standardized measurement [28]. Finally, the results of this analysis are influenced by the definitions chosen for regular and off-hours, as evidenced by our sensitivity analysis. The original definitions used in this analysis (regular hours as 9am-5pm Monday-Friday and off-hours defined as 5pm-9am Monday-Friday and weekends) were chosen to mirror regular business hours and previous analyses in the STEMI population. However, to date these have been defined arbitrarily and the ideal definitions are unknown, as evidenced by the sensitivity analysis presented here.

Conclusions

In this AHF trial, patients admitted during off-hours exhibited a distinct clinical profile, experienced greater dyspnea relief, and had lower post-discharge mortality compared with regular hours patients. These findings highlight the discordance between severity of pulmonary congestion on presentation and long-term outcomes in the AHF population. Given these results, further research into how time of presentation impacts early therapy and long-term outcomes is warranted. Furthermore, additional studies examining the circadian and neurohormonal underpinnings of these findings would be of interest in exploring the natural history of AHF. The hypothesis-generating findings presented in this study may have implications for the design and conduct of future clinical trials in AHF.

Clinical Perspective

This retrospective analysis describes the phenotype of acute heart failure patients that present during off-hours and during regular hours. It highlights a discrepancy in the natural history of heart failure where more symptomatic patients paradoxically have better long term mortality and rehospitalization rates. Despite the difference in symptomology, time of presentation does not appear to be an impediment to treatment of patients with acute heart failure.

Translational Outlook

Given the results of this analysis, future studies are necessary to determine the optimal definitions for regular and off-hours in patients with acute heart failure. In addition, the

discrepancy between dyspnea relief and traditional markers of decongestion (i.e. urine output, weight change, etc) suggests more research into the mechanisms for dyspnea relief in acute heart failure may be beneficial. Finally, this analysis has implications for the enrollment and design of future acute heart failure clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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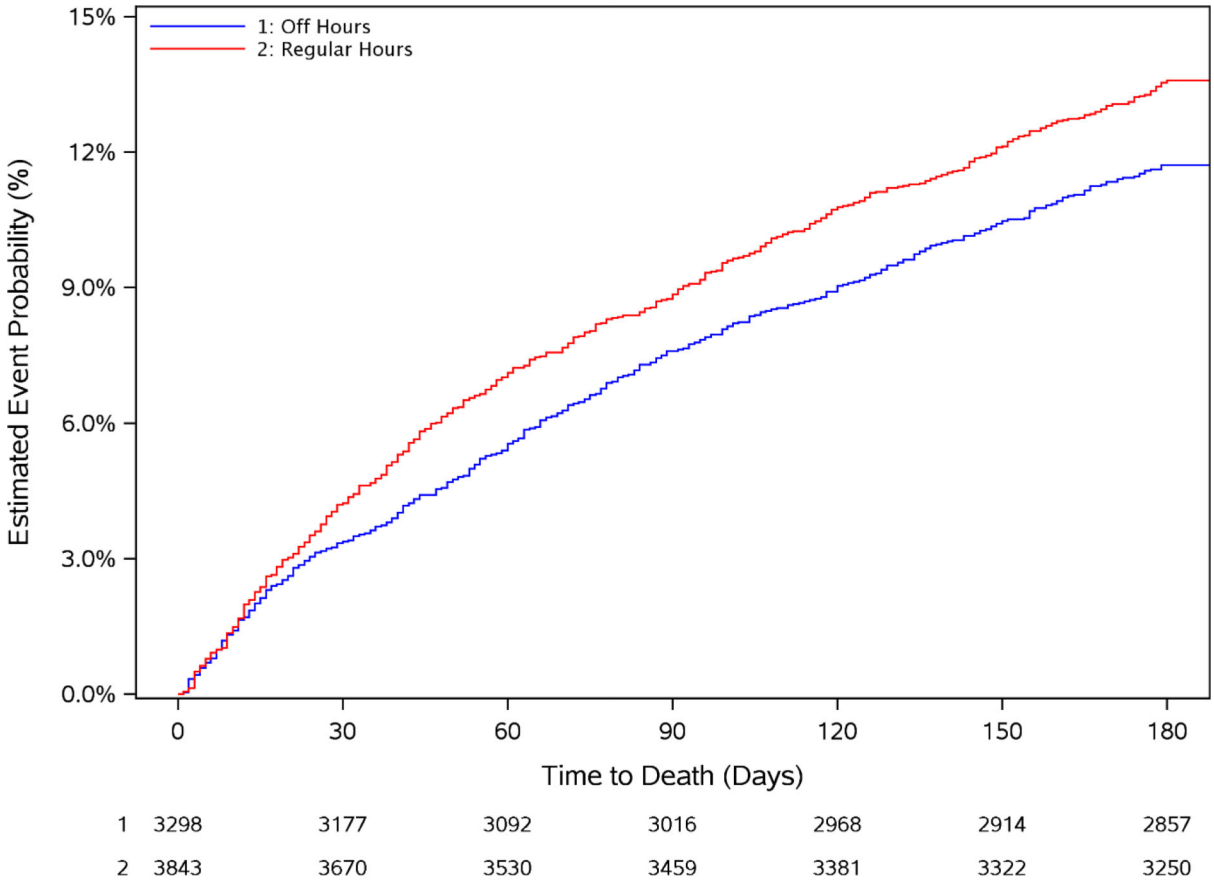

Figure 1:
180 Day Kaplan-Meier Curve by Time of Presentation

Table 1:

Baseline Patient Characteristics

	Regular Hours (N=3843)	Off-Hours (N=3298)	P-Value
Demographics			
Age, yrs (median, 25th-75th)	67 (56–76)	67 (56–77)	0.113
Female	1242 (32.3%)	1202 (36.4%)	<.001
Race Groups			0.002
White	2178 (56.7%)	1811 (54.9%)	
Black or African American	549 (14.3%)	528 (16.0%)	
Asian	977 (25.4%)	790 (24.0%)	
Other	139 (3.6%)	168 (5.1%)	
BMI, kg/m^2 (median, 25th-75th)	28 (24–33)	27 (24–32)	0.054
Systolic BP, mmHg (median, 25th-75th)	122 (110–140)	124 (110–140)	0.040
Diastolic BP, mmHg (median, 25th-75th)	75 (67–83)	74 (66–84)	0.262
Heart Rate, bpm (median, 25th-75th)	82 (72–95)	82 (72–95)	0.593
Weight, kg (median, 25th-75th)	79 (65–96)	77 (64–93)	0.007
Self-Presentation (patients were brought car, public transit, etc.)	1169/1424 (82.5%)	882/1238 (71.2%)	<.001
Emergency Services Utilized (patients brought by ambulance)	144/1424 (10.1%)	249/1238 (20.1%)	<.001
Time from presentation to randomization/study baseline, hours (median, 25th-75th)	18 (4–23)	15 (9–20)	0.039
Region			<.001
Asia Pacific	977 (25.4%)	785 (23.8%)	
Central Europe	601 (15.6%)	366 (11.1%)	
Latin America	310 (8.1%)	355 (10.8%)	
North America	1717 (44.7%)	1526 (46.2%)	
Western Europe	238 (6.2%)	268 (8.1%)	
Center Size			
High Enrolling Site	971 (25.3%)	810 (24.6%)	
Low Enrolling Site	2872 (74.7%)	2488 (75.4%)	
Orthopnea	2848 (74.2%)	2637 (80.0%)	<.001
Rales >1/3 lung fields			<.001
No Pulmonary Congestion	599 (15.6%)	341 (10.3%)	
Less than 1/3 up lung fields	1352 (35.2%)	1115 (33.8%)	
Greater than or equal to 1/3 up lung fields	1892 (49.2%)	1842 (55.9%)	
Pulmonary Edema on Chest X-Ray	2704 (78.3%)	2545 (82.3%)	<.001
JVP	2131 (55.5%)	1872 (56.8%)	0.247
Peripheral Edema	2970 (77.3%)	2360 (71.6%)	<.001
Dyspnea at Qualifying Episode			<.001
At Rest	2267 (59.0%)	2148 (65.2%)	
Minimal Activity	1576 (41.0%)	1149 (34.8%)	
NYHA Classification			0.001
NYHA Class not assessed	691 (18.0%)	557 (16.9%)	
I	117 (3.0%)	138 (4.2%)	

	Regular Hours (N=3843)	Off-Hours (N=3298)	P-Value
II	546 (14.2%)	552 (16.7%)	
III	1544 (40.2%)	1309 (39.7%)	
IV	945 (24.6%)	742 (22.5%)	
Medical History			
History of Myocardial Infarction	1369 (35.6%)	1121 (34.0%)	0.151
History of Atrial Fibrillation/Flutter	1523 (39.6%)	1151 (34.9%)	<.001
History of Hypertension	2695 (70.1%)	2455 (74.4%)	<.001
History of Diabetes Mellitus	1592 (41.4%)	1454 (44.1%)	0.023
History of Hyperlipidemia	1593 (41.5%)	1391 (42.2%)	0.528
Smoking History			0.026
Current Smoking	486 (12.7%)	477 (14.5%)	
Prior History of Smoking	1974 (51.4%)	1664 (50.5%)	
History of ICD/CRT	365 (9.5%)	275 (8.3%)	0.087
History of Cerebrovascular Disease	460 (12.0%)	382 (11.6%)	0.613
History of Peripheral Arterial Vascular Disease	403 (10.5%)	337 (10.2%)	0.711
Ejection Fraction, % (median, 25th-75th)	29 (20–35)	30 (20–37)	0.333
Ejection Fraction < 40%	2445 (82.0%)	1869 (77.9%)	<.001
Heart Failure Duration 0–1 Months	733 (23.9%)	803 (30.0%)	<.001
Heart Failure Duration, months (Median, 25th-75th)	23 (1–66)	15 (1–60)	<.001
Medication at Baseline			
ACEi or ARB	2338 (60.9%)	2002 (60.7%)	0.909
Beta Blocker	2231 (58.1%)	1927 (58.4%)	0.747
MRAs [Aldosterone Antagonists]	1157 (30.1%)	835 (25.3%)	<.001
Calcium Channel Blockers	448 (11.7%)	475 (14.4%)	<.001
Nitrates	915 (23.8%)	766 (23.2%)	0.558
Digoxin	1086 (28.3%)	809 (24.5%)	<.001
Loop Diuretics [Chronically Before QE]	2533 (66.0%)	2006 (60.9%)	<.001
Total Loop Diuretic Dose, chronically pre-qualifying episode, mg (mean, (SD))	82.6 (287.4)	73.0 (74.2)	0.72
Medication at Discharge	3222	2929	
ACEi or ARB	2264 (70.3%)	2091 (71.4%)	0.333
Beta Blocker	2190 (68.0%)	2021 (69.0%)	0.386
MRAs [Aldosterone Antagonists]	1376 (42.7%)	1192 (40.7%)	0.110
Calcium Channel Blockers	333 (10.3%)	352 (12.0%)	0.036
Nitrates	767 (23.8%)	690 (23.6%)	0.820
Digoxin	1084 (33.6%)	923 (31.5%)	0.075
Loop Diuretics	2673 (83.0%)	2445 (83.5%)	0.590
Laboratory Values			
Baseline Creatinine, mg/dL (median, 25th-75th)	1.2 (1.0–1.6)	1.2 (1.0–1.6)	0.672
Baseline GFR MDRD, ml/min (median, 25th-75th)	59 (44–75)	59 (44–75)	0.976
Baseline BUN, mg/dL (median, 25th-75th)	25 (18–38)	26 (17–39)	0.478
Baseline sodium, mmol/L (median, 25th-75th)	139 (136–141)	139 (136–141)	0.048

	Regular Hours (N=3843)	Off-Hours (N=3298)	P-Value
Baseline Potassium, mmol/L (median, 25th-75th)	4.1 (3.7–4.5)	4.0 (3.7–4.4)	0.006
Baseline Hemoglobin, g/dL (median, 25th-75th)	12.7 (11.3–14.1)	12.7 (11.4–14.0)	0.775
Baseline NT-proBNP, pg/mL (median, 25th-75th)	4460 (2015–8827)	4579 (2173–9604)	0.092
Baseline BNP, pg/mL (median, 25th-75th)	990 (536–1894)	992 (554–1819)	0.868
Treatment Group			0.704
Nesiritide	1910 (49.7%)	1654 (50.2%)	
Placebo	1933 (50.3%)	1644 (49.8%)	

Table 2:

Inpatient Therapies and 24 Hour Markers of Congestion

	Regular Hours (N=3843)	Off-Hours (N=3298)	P-Value
Diuretic Administration			
Loop Diuretics [QE to Randomization]	3321 (86.5%)	3044 (92.3%)	<.001
Loop Diuretic Dose, QE to Randomization, mg (mean, (SD))	98.4 (176.7)	97.0 (156.7)	0.002
Loop Diuretics [QE to 24Hrs Post Randomization]	3475 (90.5%)	3002 (91.1%)	0.417
Loop Diuretic Dose, QE to 24Hrs Post Randomization, mg (mean, (SD))	185.3 (239.2)	185.3 (217.4)	0.013
Number of Diuretic Medication Types Given	3494 (93.1%)	3057 (94.1%)	0.205
Furosemide Given	3574 (95.2%)	3132 (96.4%)	0.011
Torsemide Given	273 (7.3%)	159 (4.9%)	<.001
Bumetanide Given	170 (4.5%)	150 (4.6%)	0.858
Other Diuretic Use			
Thiazides Given	276 (7.2%)	198 (6.0%)	0.046
All Others Given	145 (3.8%)	116 (3.5%)	0.567
Vasodilator Use			
IV Nitroglycerin Given	430 (11.2%)	577 (17.5%)	<.001
IV Nitroprusside Given	49 (1.3%)	33 (1.0%)	0.277
Inotrope Use			
Dobutamine Given	118 (3.1%)	113 (3.4%)	0.399
Dopamine Given	47 (1.2%)	41 (1.2%)	0.941
Levosimendan Given	2 (0.1%)	1 (0.0%)	1.000
Milrinone Given	0 (0.0%)	2 (0.1%)	0.213
Vasopressor Use			
Epinephrine Given	0 (0.0%)	2 (0.1%)	0.213
Norepinephrine Given	2 (0.1%)	3 (0.1%)	0.672
Markers of Congestion			
Change in SBP, Baseline to 24Hrs (median, 25th-75th)	−10 (−20–0)	−10 (−22–1)	0.860
Change in DBP, Baseline to 24Hrs (median, 25th-75th)	−5 (−14–1)	−6 (−14–1)	0.706
Change in Creatinine, Baseline to 24Hrs, mg/dL (median, 25th-75th)	0.00 (−0.10–0.15)	0.01 (−0.10–0.15)	0.919
Urine Volume, Baseline to 24Hrs, mL (median, 25th-75th)	2300 (1600–3400)	2200 (1525–3200)	0.003
Absolute change in weight in kg from baseline to 24 hours (median, 25^{th}-75^{th})	−1.0 (−2.2–0.0)	−1.0 (−2.0–0.0)	0.003
Percent change in weight in from baseline to 24 hours (median, 25^{th}-75^{th})	−1.4 (−2.9–0.0)	−1.3 (−2.9–0.0)	0.016
Renal Function			
Absolute change in BUN in mmol/L from baseline to 24 hours (median, 25^{th}-75^{th})	0.1 (−0.8–1.4)	0.4 (−0.9–1.8)	0.037
Absolute change in creatinine in umol/L from baseline to 24 hours (median, 25^{th}-75^{th})	0.0 (−8.8–12.4)	0.0 (−8.8–12.0)	0.301

Table 3:

Association between Time of Presentation (Off hours vs. Regular Hours) and Clinical Outcomes

	Raw Event Rate (# Events/Sample Size)		Unadjusted*		Adjusted†	
	Off-Hours	**Regular Hours**	**Odds Ratio (95% CI)**	**P-value**	**Odds Ratio (95% CI)**	**P-value**
Dyspnea Relief at 24 Hours‡			1.15 (1.05–1.25)	0.002	1.14 (1.04–1.24)	0.005
30 Day All-cause Mortality/All Cause Rehosp	482/3298 (14.6%)	585/3843 (15.2%)	0.92 (0.81–1.05)	0.215	0.93 (0.81–1.07)	0.321
30 Day All-cause Mortality	111/3298 (3.4%)	162/3843 (4.2%)	0.77 (0.60–0.98)	0.034	0.74 (0.57–0.96)	0.025
30 Day All-cause Rehosp	380/3298 (11.5%)	446/3843 (11.6%)	0.96 (0.83–1.11)	0.567	0.97 (0.84–1.14)	0.741
180 Day All-Cause Mortality	383/3298 (11.6%)	517/3843 (13.4%)	0.83 (0.72–0.94)	0.005	0.82 (0.72–0.94)	0.005

*Unadjusted model controls for region.

†Adjusted model controls for region age, gender, BMI, EF, NYHA class, HR, SBP, Na, sCr, BUN, comorbidities (CAD, afib, DMII, CKD, COPD), baseline medications (beta-blocker, ACEI/ARB, MRA, digoxin, inotropes), treatment assignment (nesiritide vs placebo), and site enrollment volume.

‡Ordinal logistic regression model fit. Assuming proportional odds, the odds ratio is interpreted as the likelihood of increasing from a lower level of dyspnea response to a higher level of dyspnea response in off hours patients, compared with regular hours patients.

Table 4:

Association between Time of Presentation (Off hours vs. Regular Hours) and Clinical Outcomes Using Alternate Group Definitions*

	Raw Event Rate (# Events/Sample Size)		Unadjusted†		Adjusted‡	
	Off-Hours	**Regular Hours**	**Odds Ratio (95% CI)**	**P-value**	**Odds Ratio (95% CI)**	**P-value**
Dyspnea Relief at 24 Hours§			1.19 (1.08–1.31)	<.001	1.18 (1.07–1.30)	<.001
30 Day All-cause Mortality/All Cause Rehosp	335/2216 (15.1%)	732/4925 (14.9%)	0.99 (0.86–1.14)	0.904	1.05 (0.91–1.22)	0.507
30 Day All-cause Mortality	80/2216 (3.6%)	193/4925 (3.9%)	0.89 (0.68–1.16)	0.387	0.88 (0.67–1.17)	0.392
30 Day All-cause Rehosp	262/2216 (11.8%)	564/4925 (11.5%)	1.01 (0.86–1.18)	0.901	1.07 (0.91–1.26)	0.401
180 Day All-Cause Mortality	267/2216 (12.1%)	633/4925 (12.9%)	0.90 (0.78–1.04)	0.171	0.92 (0.80–1.07)	0.291

*Regular hours defined as 7am-7pm Monday-Friday and off-hours as 7pm-7am Monday-Friday and weekends

†Unadjusted model controls for region.

‡Adjusted model controls for region age, gender, BMI, EF, NYHA class, HR, SBP, Na, sCr, BUN, comorbidities (CAD, afib, DMII, CKD, COPD), baseline medications (beta-blocker, ACEI/ARB, MRA, digoxin, inotropes), treatment assignment (nesiritide vs placebo), and site enrollment volume.

§Ordinal logistic regression model fit. Assuming proportional odds, the odds ratio is interpreted as the likelihood of increasing from a lower level of dyspnea response to a higher level of dyspnea response in off hours patients, compared with regular hours patients.