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Is Time of the Essence? The Impact of Time of Hospital Presentation in Acute Heart Failure

Insights From ASCEND-HF Trial

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ABSTRACT

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

BACKGROUND Time of hospital presentation has been shown to impact outcomes among patients hospitalized with many conditions. However, the association among time of presentation and patient characteristics, management, and clinical outcomes among patients hospitalized with AHF has not been well characterized.

METHODS A post hoc analysis of the ASCEND-HF trial was performed, which enrolled 7,141 patients hospitalized for AHF. Patients were divided based on when they presented to the hospital; regular hours were defined as 9 AM to 5 PM, Monday through Friday, and off hours were defined as 5 PM to 9 AM, Monday through Friday and weekends. Clinical characteristics and outcomes were compared by time of presentation.

RESULTS Overall, 3,298 patients (46%) presented during off hours. Off-hour patients were more likely to have orthopnea (80% vs. 74%, respectively) and rales (56% vs. 49%, respectively) than regular-hour patients. Off-hour patients were more likely to receive intravenous (IV) nitroglycerin (18% vs. 11%, respectively) and IV loop diuretics (92% vs. 86%, respectively) as initial therapy and reported greater relief from dyspnea at 24 h (odds ratio [OR]: 1.14; 95% confidence interval [CI]: 1.04 to 1.24; $p = 0.01$) than regular-hour patients. After adjustment, off-hour presentation was associated with significantly lower 30-day mortality (OR: 0.74; 95% CI: 0.57 to 0.96; $p = 0.03$) and 180-day mortality (hazard ratio [HR]: 0.82; 95% CI: 0.72 to 0.94; $p = 0.01$) but similar 30-day rehospitalization rates ($p = 0.40$).

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 than regular-hour patients. These findings have implications for future AHF trials. (J Am Coll Cardiol HF 2018;6:298–307) © 2018 by the American College of Cardiology Foundation.

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Time of presentation to the hospital may influence health care quality and patient outcomes. In cardiology, this concept is best recognized in the context of ST-segment 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 have also been observed for patients admitted for primary arrhythmia, ruptured aortic aneurysm, acute pulmonary embolism, and noncardiac conditions (2,3). However, despite the fact that heart failure (HF) is a leading cause of hospitalization annually in the United States (4), data regarding the influence of time of presentation in patient profiles 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 heart failure (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 to 24 h) (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 night were more symptomatic than those presenting during daytime but had lower 180-day mortality (11), suggesting important differences in AHF patients presenting during regular hours and those presenting at off hours.

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

ABBREVIATIONS AND ACRONYMS

AHF = acute heart failure

HF = heart failure

HR = hazard ratio

OR = odds ratio

STEMI = ST-segment elevation myocardial infarction

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 that examined the short- and long-term efficacy and safety of nesiritide, a recombinant natriuretic peptide. The trial enrolled 7,141 patients hospitalized for AHF with a reduced or preserved ejection fraction, as shown by dyspnea with minimal activity or at rest, >1 accompanying sign, and >1 objective measurement. Patients were randomized to treatment (i.e., study baseline) with nesiritide or placebo, in addition to standard therapy, within 24 h of the first intravenous therapy for HF. Exclusion criteria included a high likelihood of being discharged from the hospital in <24 h 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 2 groups

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TABLE 1 Baseline Patient Characteristics

	Regular Hours (n = 3,483)	Off Hours (n = 3,298)	p Value
Demographics			
Age, yrs	67 (56–76)	67 (56–77)	0.113
Females	1,242 (32.3)	1,202 (36.4)	<0.001
Race groups			0.002
White	2,178 (56.7)	1,811 (54.9)	
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	28 (24–33)	27 (24–32)	0.054
Systolic blood pressure, mm Hg	122 (110–140)	124 (110–140)	0.040
Diastolic blood pressure, mm Hg	75 (67–83)	74 (66–84)	0.262
Heart rate, beats/min	82 (72–95)	82 (72–95)	0.593
Weight, kg	79 (65–96)	77 (64–93)	0.007
Self-presentation (patients were brought by car, public transit, and other)	1,169/1,424 (82.5)	882/1,238 (71.2)	<0.001
Emergency services used (patients were brought by ambulance)	144/1,424 (10.1)	249/1,238 (20.1)	<0.001
Median time from presentation to randomization/study baseline, h	18 (4–23)	15 (9–20)	0.039
Region			<0.001
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	1,717 (44.7)	1,526 (46.2)	
Western Europe	238 (6.2)	268 (8.1)	
Center size			
High enrolling site	971 (25.3)	810 (24.6)	
Low enrolling site	2,872 (74.7)	2,488 (75.4)	
Orthopnea	2,848 (74.2)	2,637 (80.0)	<0.001
Rales >1/3 lung fields			<0.001
No pulmonary congestion	599 (15.6)	341 (10.3)	
<1/3 up lung fields	1,352 (35.2)	1,115 (33.8)	
≥1/3 up lung fields	1,892 (49.2)	1,842 (55.9)	
Pulmonary edema on radiography	2,704 (78.3)	2,545 (82.3)	<0.001
JVP	2,131 (55.5)	1,872 (56.8)	0.247
Peripheral edema	2,970 (77.3)	2,360 (71.6)	<0.001
Dyspnea at qualifying episode			<0.001
At rest	2,267 (59.0)	2,148 (65.2)	
Minimal activity	1,576 (41.0)	1,149 (34.8)	
NYHA functional class			0.001
Not assessed	691 (18.0)	557 (16.9)	
I	117 (3.0)	138 (4.2)	
II	546 (14.2)	552 (16.7)	
III	1,544 (40.2)	1,309 (39.7)	
IV	945 (24.6)	742 (22.5)	
Medical history			
Myocardial infarction	1,369 (35.6)	1,121 (34.0)	0.151
Atrial fibrillation/flutter	1,523 (39.6)	1,151 (34.9)	<0.001
Hypertension	2,695 (70.1)	2,455 (74.4)	<0.001
Diabetes mellitus	1,592 (41.4)	1,454 (44.1)	0.023
Hyperlipidemia	1,593 (41.5)	1,391 (42.2)	0.528
Smoking			0.026
Current smoking	486 (12.7)	477 (14.5)	
Previous smoking	1,974 (51.4)	1,664 (50.5)	
ICD/CRT	365 (9.5)	275 (8.3)	0.087

Continued on the next page

based on time of presentation to the hospital (defined as when they registered at the hospital). Regular hours were defined as 9 AM to 5 PM, Monday through Friday, and off hours were defined as 5 PM to 9 AM, Monday through Friday and weekends. These cutoffs were chosen to reflect the typical hours of outpatient clinics, and regular business activity, and clinical trial enrollment; and to mirror similar analyses in the STEMI population (1,3,14). As a sensitivity analysis, outcome analyses were repeated with regular hours defined as 7 AM to 7 PM, Monday through Friday, and off hours defined as 7 PM to 7 AM Monday through Friday and weekends (11).

Relief from dyspnea was measured using a self-reported form consisting of a 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 death 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, laboratory values, and medication use, were described for those presenting during regular hours versus off hours by using median (25th to 75th percentiles) for continuous variables and frequency (percent) for categorical variables. Comparisons between groups of time of presentation were performed using 2-sided Wilcoxon rank sum tests for continuous variables and chi-square tests for categorical variables, and the threshold for statistical significance was a p value <0.05. Similar approaches were used to investigate the associations between time of presentation inpatient therapies and 24-h markers of congestion. Ordinal logistic regression models were used to assess the association of time of presentation to dyspnea relief at 24 h. 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 used in ASCEND-HF mortality and dyspnea models or added a priori according to clinical judgment (15,16). The method of multiple imputations was used to impute missing data for the adjustment variables, assuming that data were missing at random. Ten multiply-imputed datasets were used, and generally, the rate of missingness for all variables was <10%.

Logistic regression models were used to assess the association among time of presentation and 30-day mortality and rehospitalization, 30-day mortality, and 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 were defined as 7 PM to 7 AM, Monday through Friday and weekends, while regular-hour patients were those presenting from 7 AM to 7 PM, Monday through 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 used Akaike information criteria to compare model 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 2-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 version 9.4 software (Cary, North Carolina). A 2-tailed p value <0.05 was considered statistically significant.

TABLE 1 Continued

	Regular Hours (n = 3,483)	Off Hours (n = 3,298)	p Value
Cerebrovascular disease	460 (12.0)	382 (11.6)	0.613
Peripheral arterial vascular disease	403 (10.5)	337 (10.2)	0.711
Median ejection fraction	29 (20–35)	30 (20–37)	0.333
Ejection fraction <40%	2,445 (82.0)	1,869 (77.9)	<0.001
Heart failure duration 0–1 month	733 (23.9)	803 (30.0)	<0.001
Median heart failure duration, months	23 (1–66)	15 (1–60)	<0.001
Medication at baseline			
ACEi or ARB	2,338 (60.9)	2,002 (60.7)	0.909
Beta-blocker	2,231 (58.1)	1,927 (58.4)	0.747
MRAs (aldosterone antagonists)	1,157 (30.1)	835 (25.3)	<0.001
Calcium channel blockers	448 (11.7)	475 (14.4)	<0.001
Nitrates	915 (23.8)	766 (23.2)	0.558
Digoxin	1,086 (28.3)	809 (24.5)	<0.001
Loop diuretics (chronically before QE)	2,533 (66.0)	2,006 (60.9)	<0.001
Total loop diuretic dose, chronically pre-qualifying episode, mg	82.6 ± 287.4	73.0 ± 74.2	0.72
Medication at discharge	n = 3,222	n = 2,929	
ACE inhibitor or ARB	2,264 (70.3)	2,091 (71.4)	0.333
Beta-blocker	2,190 (68.0)	2,021 (69.0)	0.386
MRAs (aldosterone antagonists)	1,376 (42.7)	1,192 (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	1,084 (33.6)	923 (31.5)	0.075
Loop diuretics	2,673 (83.0)	2,445 (83.5)	0.590
Laboratory values			
Median baseline creatinine, mg/dl	1.2 (1.0–1.6)	1.2 (1.0–1.6)	0.672
Median baseline GFR MDRD, ml/min	59 (44–75)	59 (44–75)	0.976
Median baseline BUN, mg/dl	25 (18–38)	26 (17–39)	0.478
Median baseline sodium, mmol/l	139 (136–141)	139 (136–141)	0.048
Median baseline potassium, mmol/l	4.1 (3.7–4.5)	4.0 (3.7–4.4)	0.006
Median baseline hemoglobin, g/dl	12.7 (11.3–14.1)	12.7 (11.4–14.0)	0.775
Median baseline NT-proBNP, pg/ml	4,460 (2,015–8,827)	4,579 (2,173–9,604)	0.092
Median baseline BNP, pg/ml	990 (536–1,894)	992 (554–1,819)	0.868
Treatment group			0.704
Nesiritide	1,910 (49.7)	1,654 (50.2)	
Placebo	1,933 (50.3)	1,644 (49.8)	

Values are median (25th to 75th percentile), n (%), or mean ± SD, unless otherwise indicated.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; BUN = blood urea nitrogen; CRT = cardiac resynchronization therapy; GFR = glomerular filtration rate; ICD = implantable cardiac defibrillator; JVP = jugular venous pressure; MDRD = modification of diet in renal disease; MRAs = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; QE = qualifying event.

RESULTS

CHARACTERISTICS OF GROUPS BY TIME OF PRESENTATION. Overall, 3,298 patients (46%) presented during off hours. Patients who presented during off hours were more likely to be female, to self-report as nonwhite, and to have a history of smoking compared with regular-hour patients (Table 1). The median left ventricle ejection fractions were similar between the 2 groups, and background and discharge guideline-directed medical therapy was distributed evenly, except that regular-hour patients were more likely to be prescribed mineralocorticoid receptor antagonists. Baseline laboratory values including natriuretic peptide concentrations were similar between the 2 groups. Median times from presentation to randomization were 18 h and 15 h for regular-hour and off-hour patients, respectively (p = 0.039). There were no differences in treatment assignment. Patients presenting during off hours were more likely to use emergency services for transportation to the hospital, whereas regular-hour patients were more likely to transport themselves. The number of patients presenting to the hospital was highest on Monday, with decreasing numbers throughout the rest of the week (Online Table 1).

Patients enrolled in North America, Latin America, and Western Europe presented more frequently during off hours, whereas regular-hour patients were more common among patients enrolled in Central Europe and Asia Pacific (Online 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-hour patients were more likely to receive loop diuresis and intravenous (IV) nitroglycerin prior to randomization, but there were no between-group differences in the number of patients receiving diuretic drugs from presentation to 24 h after randomization (Table 2). Patients presenting during off hours reported significantly greater dyspnea relief at 24 h, 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 to 1.24) (Table 3). When the definition of regular hours was modified to 7 AM to 7 PM, Monday through Friday, and off hours was defined as 7 PM to 7 AM, Monday through Friday and weekends, off-hour patients were found to still have significantly more dyspnea relief at 24 h (OR: 1.18; 95% CI: 1.07 to 1.30) (Table 4) after adjustment for potential confounders. Patients in the off-hour group had significantly shorter hospitalizations (mean: 7.18 days vs. 8.04 days, respectively) than those admitted during regular hours, even after adjustment for covariates (OR: 0.93; 95% CI: 0.89 to 0.95) (Online Table 2). A 2-way interaction analysis demonstrated that the association between time of presentation and length of hospitalization was not modified by geographic region ($p = 0.60$ after adjustment) (Online 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 to 0.96; $p = 0.03$) (Table 3). Overall, 30-day readmission rates were similar between the 2 groups, and there were no differences between the groups in the composite endpoint of mortality and rehospitalization. Off-hour patients were at significantly decreased risk of 180-day mortality than regular-hour patients after adjustment (HR: 0.83; 95% CI: 0.72 to 0.94; $p = 0.01$) (Table 3, Figure 1). When a sensitivity analysis was performed to change the definitions of regular hours to 7 AM to 7 PM, Monday through Friday and off hours to 7 PM to 7 AM, Monday through Friday and weekends, the differences in 30- and 180-day mortality between off-hour and regular-hour patients were not statistically significant after adjustment ($p = 0.39$ for 30-day mortality; $p = 0.29$ for 180-day mortality) (Table 4). For sensitivity analysis, off-hour and regular-hour patients had similar rates of 30-day rehospitalization, composite endpoints 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-hour patients were more likely to receive loop diuretics and nitroglycerin as part of initial therapy and reported more relief from dyspnea 24 h after randomization. There were no differences between groups in the composite of 30-day mortality and rehospitalization. However, off-hour 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 (e.g., rales, orthopnea, dyspnea at rest, pulmonary edema on chest radiographs), whereas patients admitted during regular hours were more likely to have signs of systemic congestion (e.g., 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 finding differs from that in a prior analysis of ASCEND-HF that found resting dyspnea correlated with 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 pathophysiological basis of these patients having better long-term survival. In the present analysis, off-hour and regular-hour 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 h post-randomization. This is in contrast to the STEMI population, in whom door-to-balloon times and overall survival are impacted by time of presentation (1,3). Although 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-hour patients received slightly more diuretics and significantly more IV nitroglycerin between presentation and randomization and experienced increased dyspnea relief at 24 h, 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 IV 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-hour and regular-hour patients had clinically similar markers of decongestion (e.g., urine output, body weight change at 24 h) 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 (i.e., than 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 be explained by age, renal function, or natriuretic peptides. Given those 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 RELAX-AHF (serelaxin, Novartis, Basel, Switzerland), recombinant human relaxin-2, for Treatment of Acute Heart Failure, in which nighttime patients had a lower risk of 180-day mortality that was statistically significant after multivariate adjustment (11). However, in the present analysis, sensitivity analyses with modified group definitions exactly matching those used by the RELAX-AHF investigators (off-hour defined as 7 PM to 7 AM, Monday through Friday and weekends) failed to demonstrate statistically significant differences in outcomes, with similar 30- and 180-day risks of mortality among off-hour and regular-hour patients. Although these varying results between the present

TABLE 2 Inpatient Therapies and 24-h Markers of Congestion

	Regular Hours (n = 3,483)	Off Hours (n = 3,298)	p Value
Diuresis administration			
Loop diuretic drugs (QE to randomization)	3,321 (86.5)	3,044 (92.3)	<0.001
Loop diuretic dose, QE to randomization, mg	98.4 (176.7)	97.0 (156.7)	0.002
Loop diuretics (QE to 24-h post-randomization)	3,475 (90.5)	3,002 (91.1)	0.417
Loop diuretic dose, QE to 24-h post-randomization, mg	185.3 (239.2)	185.3 (217.4)	0.013
Number of diuretic medication types given	3,494 (93.1)	3,057 (94.1)	0.205
Mean furosemide	3,574 (95.2)	3,132 (96.4)	0.011
Torsemide	273 (7.3)	159 (4.9)	<0.001
Bumetanide	170 (4.5)	150 (4.6)	0.858
Other diuretics used			
Thiazides	276 (7.2)	198 (6.0)	0.046
All others	145 (3.8)	116 (3.5)	0.567
Vasodilator used			
IV nitroglycerin	430 (11.2)	577 (17.5)	<0.001
IV nitroprusside	49 (1.3)	33 (1.0)	0.277
Inotrope used			
Dobutamine	118 (3.1)	113 (3.4)	0.399
Dopamine	47 (1.2)	41 (1.2)	0.941
Levosimendan	2 (0.1)	1 (0.0)	1.000
Milrinone	0 (0.0)	2 (0.1)	0.213
Vasopressor used			
Epinephrine	0 (0.0)	2 (0.1)	0.213
Norepinephrine	2 (0.1)	3 (0.1)	0.672
Markers of congestion			
Change in systolic blood pressure, baseline to 24 h	−10 (−20 to 0)	−10 (−22 to 1)	0.860
Change in diastolic blood pressure, baseline to 24-h	−5 (−14 to 1)	−6 (−14 to 1)	0.706
Change in creatinine, baseline to 24 h, mg/dl	0.00 (−0.10 to 0.15)	0.01 (−0.10 to 0.15)	0.919
Urine volume, baseline to 24 h, ml	2,300 (1,600 to 3,400)	2,200 (1,525 to 3,200)	0.003
Absolute change in weight, kg, from baseline to 24 h	−1.0 (−2.2 to 0.0)	−1.0 (−2.0 to 0.0)	0.003
Percent change in weight, kg, from baseline to 24 h	−1.4 (−2.9 to 0.0)	−1.3 (−2.9 to 0.0)	0.016
Renal function			
Absolute change in BUN in mmol/l from baseline to 24 h	0.1 (−0.8 to 1.4)	0.4 (−0.9 to 1.8)	0.037
Absolute change in creatinine, μmol/l from baseline to 24 h	0.0 (−8.8 to 12.4)	0.0 (−8.8 to 12.0)	0.301

Values are n (%) or median (25th to 75th percentile), unless otherwise indicated.
Abbreviations as in Table 1.

TABLE 3 Association Between Time of Presentation (Off Hours vs. Regular Hours) and Clinical Outcomes

	Raw Event Rate (Number of 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 h‡			1.15 (1.05–1.25)	0.002	1.14 (1.04–1.24)	0.005
30-day all-cause mortality/all cause rehospitalization	482/3,298 (14.6)	585/3,483 (15.2)	0.92 (0.81–1.05)	0.215	0.93 (0.81–1.07)	0.321
30-day all-cause mortality	111/3,298 (3.4)	162/3,483 (4.2)	0.77 (0.60–0.98)	0.034	0.74 (0.57–0.96)	0.025
30-day all-cause rehospitalization	380/3,298 (11.5)	446/3,483 (11.6)	0.96 (0.83–1.11)	0.567	0.97 (0.84–1.14)	0.741
180-day all-cause mortality	383/3,298 (11.6)	517/3,483 (13.4)	0.83 (0.72–0.94)	0.005	0.82 (0.72–0.94)	0.005

Values are n/N (%), unless otherwise indicated. *Unadjusted model controls for region. †Adjusted model controls for region age, gender, BMI, ejection fraction, NYHA class, heart rate, systolic blood pressure, Na, sCr, BUN, comorbidities (coronary artery disease, atrial fibrillation, DMII, chronic kidney disease, chronic obstructive kidney disease), 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-hour patients compared with regular-hour patients.

Abbreviations as in Table 1.

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-hour 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

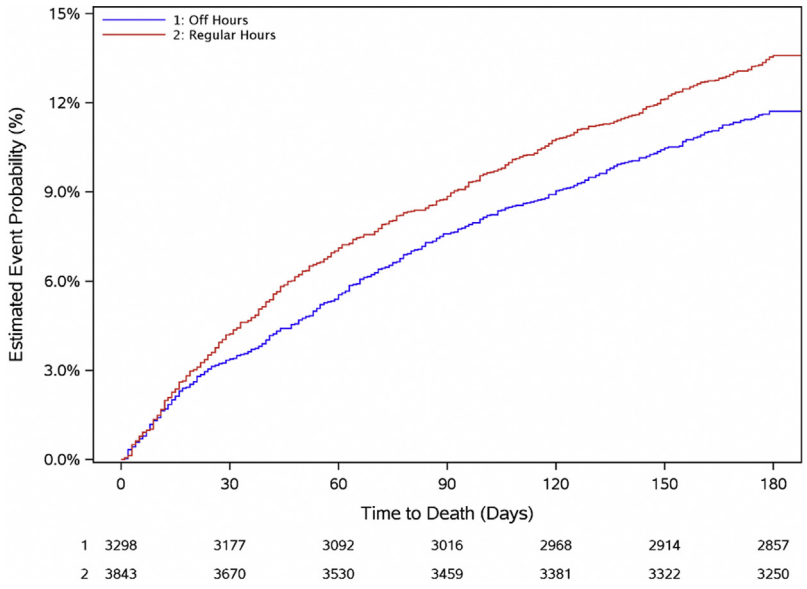
TABLE 4 Association Between Time of Presentation (Off Hours vs. Regular Hours) and Clinical Outcomes Using Alternate Group Definitions*

	Raw Event Rate (Number or 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 h§			1.19 (1.08–1.31)	<0.001	1.18 (1.07–1.30)	<0.001
30-day all-cause mortality/all cause rehospitalization	335/2,216 (15.1)	732/4,925 (14.9)	0.99 (0.86–1.14)	0.904	1.05 (0.91–1.22)	0.507
30-day all-cause mortality	80/2,216 (3.6)	193/4,925 (3.9)	0.89 (0.68–1.16)	0.387	0.88 (0.67–1.17)	0.392
30-day all-cause rehospitalization	262/2,216 (11.8)	564/4,925 (11.5)	1.01 (0.86–1.18)	0.901	1.07 (0.91–1.26)	0.401
180-day all-cause mortality	267/2,216 (12.1)	633/4,925 (12.9)	0.90 (0.78–1.04)	0.171	0.92 (0.80–1.07)	0.291

Values are n/N (%), unless otherwise indicated. *Regular hours were defined as 7 AM to 7 PM, Monday through Friday, and off hours as 7 PM to 7 AM, Monday through Friday and weekends. †Unadjusted model controls for region. ‡Adjusted model controls for region age, gender, BMI, EF, NYHA class, HR, systolic blood pressure, 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-hour patients compared with regular-hour patients.

Abbreviations as in Tables 1 and 3.

FIGURE 1 180-Day Kaplan-Meier Curve by Time of Presentation



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 h after first IV HF therapy, if future trials mandate enrollment very early (i.e., a few hours) after presentation, our results suggest that dedicating substantial trial staff and resources for off-hour enrollment may be offset by lower post-discharge event rates among off-hour patients. Furthermore, increased dyspnea relief in off-hour patients may hinder the ability of an investigational therapy to show a benefit for dyspnea over that for 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.

STUDY LIMITATIONS. There are several limitations to the data inherent to exploratory analyses. First, this analysis is limited to the pre-specified 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. Second, many baseline characteristics were gathered at time of randomization, which was on average 18 and 15 h after time of initial presentation for regular- and off-hour 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 Third, conclusions are subject to the intrinsic biases secondary to post hoc analyses, including residual confounding. Fourth, some of the measurements are subjective, particularly data for dyspnea relief, which lacks a universally agreed upon standardized measurement (28). Finally, results of this analysis are influenced by the definitions chosen for regular and off hours, as shown by our sensitivity analysis. The original definitions used in this analysis (regular hours as 9 AM to 5 PM, Monday through Friday, and off hours as 5 PM to 9 AM, Monday through Friday and weekends) were chosen to mirror regular business hours and previous analyses in the STEMI population. However, to date these parameters have been defined arbitrarily, and the ideal definitions are unknown, as shown by the sensitivity analysis presented here.

CONCLUSIONS

In this AHF trial, patients who were admitted during off hours exhibited a distinct clinical profile, experienced greater dyspnea relief, and had lower post-discharge mortality than regular-hour 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.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: This retrospective analysis describes the phenotype of acute heart failure patients who presented during off hours and those who presented during regular hours. Analysis highlighted a discrepancy in the natural history of heart failure, where more symptomatic patients paradoxically had lower long-term mortality and rehospitalization rates. Despite differences in symptoms, 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 conventional markers of decongestion (i.e., urine output, weight change, and so forth) suggests more research of 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.

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KEY WORDS heart failure, presentation, ASCEND-HF

APPENDIX For supplemental tables and a figure, please see the online version of this article.