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ORIGINAL PAPER

Early Vasoactive Drugs Improve Heart Failure Outcomes

Vasoactive therapy is often used to treat acute decompensated heart failure (ADHF). The authors sought to determine whether clinical outcomes are temporally associated with time to vasoactive therapy (vasoactive time) in ADHF. Using the Acute Decompensated Heart Failure (ADHERE) Registry, the authors examined the relationship between vasoactive time and inpatient mortality within 48 hours of hospitalization. Vasoactive agents were used early (defined as <6 hours) in 22,788 (63.8%) patients and late in 12,912 (36.2%). Median vasoactive time was 1.7 and 14.7 hours in the early and late groups, respectively. In-hospital mortality was significantly lower in the early group (odds ratio, 0.87; 95% confidence interval, 0.79–0.96; P=.006), and the adjusted odds of death increased 6.8% for every 6 hours of treatment delay (95% confidence interval, 4.2–9.6; P<.0001). Early vasoactive initiation is associated with improved outcomes in patients hospitalized for ADHF. Congest Heart Fail. *2009;15:256–264.* ©*2009 Wiley Periodicals, Inc.*

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Hospitalization for acute decompensated heart failure (ADHF) is common in the United States.[1] In 2003, 1,093,000 hospital discharges with a diagnosis of heart failure were reported. Hospitalizations for ADHF are associated with significant mortality and morbidity. The total 2003 mortality due to heart failure is estimated at 57,218.[1] Large observational registry data suggest that the in-hospital and short-term (60–90 days) mortality rates after a heart failure hospitalization are approximately 4% and 13%, respectively.[2,3] These data underscore the need to identify factors that may influence the clinical outcomes of patients hospitalized for ADHF.

Elevated left ventricular filling pressures may contribute to the pathophysiology and progression of heart failure through several potential mechanisms.[4] Studies of implanted hemodynamic monitoring systems reveal that patients with ADHF experience increases in filling pressures days before presentation with acute symptoms.[5,6] Thus, pathophysiologic processes that can result in adverse outcomes or heart failure progression are fully activated in most ADHF patients at or before the time of presentation. Based on these concepts, we hypothesized that early vasoactive therapy administration may be more effective at reducing symptoms and improving outcomes as compared with late administration. However, this concept has not been adequately studied.[2] This study's objective was to determine the association between clinical outcomes and the time to vasoactive therapy initiation in patients hospitalized for ADHF.

Methods

The Acute Decompensated Heart Failure (ADHERE) National Registry database was analyzed for this study. The design, methods, and initial ADHERE results have been published.[3,7–9] ADHERE is a large, national, multicenter registry designed to collect data on the clinical characteristics, treatment patterns, and outcomes of patients hospitalized for ADHF.[3] Data were collected from participating hospitals across the United States. Hospitals of various sizes from all regions of the country were represented. All hospitals obtained institutional review board or ethics board approval for participation. The data collection system was designed such that patient informed consent was not necessary.[3]

Patient episodes were included if they received an intravenous (IV) vasoactive agent (nesiritide, nitroglycerin, nitroprusside, dobutamine, dopamine, or milrinone) within the first 48 hours of the hospitalization. The 48 hours limitation time point was established arbitrarily for this analysis in an attempt to differentiate between patients who received vasoactive agents as part of the initial management strategy for ADHF and those who might have received vasoactive therapy for other reasons. Delayed therapy may be appropriately used for indications or complications not present at the time of admission (eg, post-admission myocardial infarction) or for failure to respond to initial therapy. Our goal was to focus on a homogenous group of patients with a similar diagnosis and indication for vasoactive therapy. To eliminate competing needs for vasoactive treatment among patients hospitalized with both ADHF and acute coronary syndromes, patients with an admitting or discharge (either primary

or secondary) diagnosis of acute myocardial infarction, elevated troponin (troponin I ≥1 ng/mL or positive if a qualitative test), or creatine kinase–MB >5% were excluded.

A relationship between mortality and time to vasoactive treatment was examined using locally weighted scatterplot smoothing (LOWESS).[10] Prior to analysis, it was hypothesized that vasoactive use initiated during the first several hours (≤8 hours) after presentation would be of greatest benefit. The LOWESS plot depicting mortality for patients on any vasoactive agents indicated that even a shorter period (≤6 hours) would be appropriate. Eligible patients were categorized into 2 groups depending on the timing of vasoactive therapy administration: early administration (≤6 hours) and late administration (6–48 hours). Demographics, medical history, clinical characteristics, and outcomes (mortality, length of stay, intensive care unit (ICU) admission, and ICU length of stay) were summarized and compared between groups using analysis of variance, Wilcoxon, and chi-square tests, as appropriate. Two-sided *P* values were reported. Five descriptive variables had >2% missing data (race, 3%; prior myocardial infarction and congestion, 9%; quantitative ejection fraction, 20%; B-type natriuretic peptide, 47%). Multiple logistic regression was utilized to adjust mortality comparisons for known risk factors of age, dyspnea at rest, heart rate, systolic blood pressure, diastolic blood pressure, blood urea nitrogen, creatinine, and sodium.[11] Observations with missing covariates were excluded from adjusted analysis. Less than 2% of blood urea nitrogen, serum creatinine, and serum sodium data were missing, and <1% of blood pressure and heart rate data were missing. Time to first vasoactive treatment was analyzed as a continuous and as a dichotomous variable. Adjusted odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were computed for mortality comparisons of patients taking vasoactives early (≤6 hours) with patients taking vasoactives after 6, 12, 18, 24, or 30 hours. The area under the receiver operator curve (AUC) was used to assess model discrimination. Subgroups of patients taking only inotropes and only vasodilators were examined separately. All analyses were carried out using SAS version 8.2 (SAS Institute, Cary, NC) with exception of LOWESS (procedure PLSMO from Hmisc library for S-PLUS provided by FE Harrell).

Results

The ADHERE database contained data on 163,457 hospital admissions from 288 hospitals as of May 2005. Of these, 46,811 (29%) patient episodes received IV vasoactive agents during hospitalization. Vasoactive agents were used after 48 hours in 5765, only 12%, of all hospital admission episodes with vasoactive use. Time to vasoactive treatment was missing for 113 (0.2%) hospitalizations. In the remaining 40,933 patient episodes, the first vasoactive agent was used within 48 hours of admission. Out of these, the following subgroups were excluded sequentially in the order shown: (1) 3125 hospitalizations with diagnoses of acute myocardial infarction, (2) 1906 episodes with elevated troponin T or I, and (3) 202 hospitalizations with creatine kinase–MB >5%. As a result, 35,700 (76%) of 46,811 hospitalizations with vasoactive agent use were included in the analysis. As expected, the distribution of time to first vasoactive agent was skewed with median time of 3.7 hours (interquartile range [IQR], 1.2–9.5 hours) and mean time of 7.9 hours (SD=10.2 hours). Vasoactive agents were used within the first 6 hours in 22,788 (64%) hospitalizations and between 6 and 48 hours in 12,912 (36%) hospitalizations. Median time to vasoactive agent initiation was 1.7 and 14.7 hours in the early and late treatment groups, respectively. The initiation of vasoactive therapy >24 but <48 hours after admission occurred in 10% of hospitalizations.

Differences in baseline characteristics were present as expected in an observational study (Table I). Evidence of pulmonary congestion (chest radiograph congestion and rales) and dyspnea at rest were more common in patients who received early compared with late administration. More patients in the late therapy group had anemia and systolic dysfunction. Blood urea nitrogen was higher and systolic blood pressure was lower in the late treatment group.

IV diuretics were prescribed in most patients. The median time to diuretic initiation was longer in the late vasoactive group (1.7 vs 3.3 hours; *P*<.0001). Inotropes were used less frequently in the early vasoactive group (31.6%) and more frequently in the late vasoactive group (43.7%; *P*<.0001). Conversely, vasodilators were used more frequently in the early vasoactive group (82.0%) and less frequently in the late vasoactive group (69.8%; *P*<.0001).

During hospitalization, a higher proportion of patients in the late administration group required cardiopulmonary resuscitation or new dialysis. More patients in the early administration group required mechanical ventilation or ultrafiltration (Table II).

In-hospital mortality did not vary by time to vasoactive initiation for patients who received vasoactive agents in the first 6 hours after presentation, but hospital mortality subsequently increased as the time to treatment increased (Figure 1). The in-hospital mortality rate was significantly lower in patients receiving vasoactive agents in the first 6 hours compared with those who received them after 6 hours (unadjusted OR, 0.77; *P*<.0001). The lower mortality risk observed with early vasoactive administration persisted after adjustment for age, dyspnea at rest, heart rate, systolic blood pressure, diastolic blood pressure, blood urea nitrogen, creatinine, and sodium (OR, 0.87; 95% CI, 0.79–0.96; *P*=.0055). This relationship was even more pronounced as the time interval between hospital presentation and vasoactive administration increased (Figure 2). When time to first vasoactive treatment was analyzed as a continuous variable, the adjusted odds of death increased 6.8% for every 6 hours of delay in treatment (95% CI, 4.2–9.6; *P*<.0001). The AUC of adjusted models ranged from 0.77 to 0.79, indicating adequate model discrimination.

Emergency department, in-hospital, ICU, and overall length of stays were

Table I. Baseline Demographics and Clinical Characteristics

Variable	Early Administration n=22,788	Late Administration n=12,912	*P* Value
Demographics			
Age, y	70.5±14	70.6±14	.4905
Male	12,242 (53.7)	7484 (58)	<.0001
Caucasian	16,390 (74.3)	9445 (75.3)	.032
Medical history			
Atrial fibrillation	7005 (30.7)	4458 (34.5)	<.0001
Coronary artery disease	14,499 (63.6)	8455 (65.5)	.0004
COPD/asthma	7043 (30.9)	4054 (31.4)	.336
Chronic dialysis	988 (4.3)	330 (2.6)	<.0001
Chronic renal insufficiency	8013 (35.2)	4973 (38.5)	<.0001
Diabetes	10,352 (45.4)	6033 (46.7)	.0182
Heart failure history	18,579 (81.5)	10,830 (83.9)	<.0001
Hyperlipidemia	9073 (39.8)	5089 (39.4)	.4558
Hypertension	16,768 (73.6)	9196 (71.2)	<.0001
Prior myocardial infarction	7772 (37.5)	4531 (37.9)	.4595
Prior stroke	3715 (16.3)	2069 (16)	.4925
Prior ventricular tachycardia/fibrillation	3015 (13.2)	1965 (15.2)	<.0001
Signs and symptoms			
Hospitalization from the emergency department	16,358 (71.8)	9729 (75.3)	<.0001
Congestion on first chest radiograph	16,321 (79.5)	8721 (73.8)	<.0001
Dyspnea at rest	9768 (42.9)	4514 (35)	<.0001
Edema	15,178 (66.6)	9093 (70.4)	<.0001
Fatigue	7306 (32.1)	4587 (35.5)	<.0001
Rales	16,283 (71.5)	8697 (67.4)	<.0001
Laboratory data and vital signs			
LVEF, %	34.1±16.9	31.5±16.2	<.0001
BUN, mg/dL	34.9±22.9	38.2±24.2	<.0001
Serum creatinine, mg/dL median (IQR)	1.5 (1.1–2.1)	1.5 (1.2–2.1)	<.0001
Sodium, mEq/L	137.8±4.8	137.3±4.9	<.0001
BNP, pg/mL median (IQR)	1040 (535–1700)	1180 (634–1940)	<.0001
Systolic blood pressure, mm Hg	147.6±41.2	134.5±32.3	<.0001
Heart rate, beats/min	90.7±23.2	86.6±21.3	<.0001
Pre-admission medications			
ACE inhibitor	9906 (43.5)	5472 (42.4)	.0456
Angiotensin receptor blocker	3091 (13.6)	1742 (13.5)	.8472
β-Blocker	13,050 (57.3)	7424 (57.5)	.6717
Digoxin	6916 (30.4)	4410 (34.2)	<.0001
Diuretic	16,896 (74.2)	10,341 (80.1)	<.0001

Abbreviations: ACE, angiotensin-converting enzyme; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; LVEF, left ventricular ejection fraction. Continuous variables are reported as mean ± SD unless otherwise specified. Categoric variables are reported as No. (%). To convert to SI units, multiply SCr × 88.4 (for μmol/L); multiply BUN × 0.357 (for mmol/L); multiply sodium × 1.0 (for mmol/L).

shorter for patients who received vasoactive agents early compared with those who received them >6 hours after presentation (Table II). A higher proportion of patients who received early administration required ICU admission. Even though more early administration patients required ICU admission, their length of stay in the ICU was shorter compared with patients who received a vasoactive agent at a later time point. More patients in the early administration group were asymptomatic at discharge compared with the late administration group.

Out of all hospitalizations with vasoactive use, 22,844 (64%) received only vasodilators and 8004 (22%) received only inotropes, with patients in the remaining hospitalizations receiving both types of vasoactive agents. Vasodilators were often initiated earlier than inotropes: median time to treatment was 3.1 (IQR, 0.9–7.9) vs 5.8 (IQR, 2.2–17.8) hours. The clinical characteristics of these groups were examined. Men were more likely to receive only inotropes. A higher proportion of inotrope-treated patients also had atrial fibrillation, chronic renal insufficiency, previous heart failure, and a history of ventricular tachycardia or ventricular fibrillation. Diabetes and hypertension were more common in the vasodilator-only group. A higher proportion of vasodilator-treated patients, compared with inotrope-treated patients, had chest radiograph congestion (80.0% vs 69.5%), dyspnea at rest (41.0% vs 35.8%), and rales (72.7% vs 63.2%). Fatigue was more prevalent among inotrope-treated patients (41.3% vs 29.2%). Average systolic blood pressure (118 vs 154 mm Hg), serum sodium (136 vs 138 mmol/L), and left

Table II. In-Hospital Procedures, Medications, and Outcomes

Variable	Early Administration n=22,788	Late Administration n=12,912	*P* Value
Non-IV medications during the hospitalization			
ACE inhibitor	13,103 (57.5)	7147 (55.4)	.0001
Angiotensin receptor blocker	3399 (14.9)	1981 (15.3)	.2785
β-Blocker	15,546 (68.2)	8923 (69.1)	.0824
Digoxin	8615 (37.8)	5632 (43.6)	<.0001
Diuretic	17,370 (76.2)	10,317 (79.9)	<.0001
In-hospital procedures			
Cardiopulmonary resuscitation	438 (1.9)	312 (2.4)	.0018
Cardiac catheterization	2676 (11.7)	1461 (11.3)	.2248
Defibrillation	255 (1.1)	182 (1.4)	.0165
Mechanical ventilation	2084 (9.1)	970 (7.5)	<.0001
New dialysis	438 (1.9)	329 (2.5)	.0001
Ultrafiltration	365 (2.3)	177 (1.9)	.0346
Clinical outcomes			
Mortality	1166 (5.1)	847 (6.6)	<.0001
Time in emergency department, h median (IQR)	4.5 (3.1, 6.5)	5.4 (3.8, 7.6)	<.0001
In-hospital length of stay, d median (IQR)	4.5 (2.8, 7.3)	5.6 (3.6, 8.8)	<.0001
Total length of stay, d median (IQR)	4.7 (3, 7.6)	5.8 (3.8, 9)	<.0001
Admitted to ICU	8622 (37.8)	3740 (29.0)	<.0001
ICU time, d median (IQR)	2.4 (1.3, 4)	3 (1.9, 5.4)	<.0001
Asymptomatic at discharge	10,016 (51.9)	5012 (46.7)	<.0001

Abbreviations: ACE, angiotensin-converting enzyme; ICU, intensive care unit; IQR, interquartile range; IV, intravenous. Continuous variables are reported as median (IQR). Categoric variables are reported as No. (%).

ventricular ejection fraction (27% vs 36%) were significantly lower in patients treated with inotropes. Mean blood urea nitrogen (43.5 vs 32.3 mg/dL) and median serum creatinine (1.6 vs 1.4 mg/dL) values were significantly higher in patients who received inotropes compared with vasodilators.

The relationship between mortality and time to treatment appeared to be different for patients treated exclusively with vasodilators and for those treated with inotropes only (Figure 1). Inotropes were associated with a high initial mortality that dropped by 6 hours and then steadily increased to 48 hours. Vasodilators were associated with a low initial mortality that gradually increased throughout the first 24 hours and then remained constant.

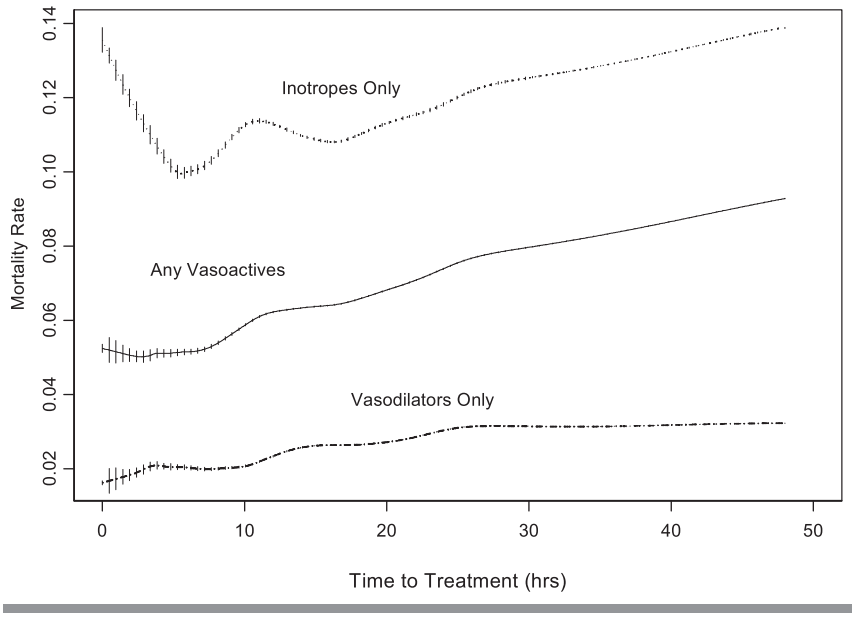

Figure 1. Mortality by time to first vasoactive agent overall and by type of vasoactive agent. The line represents locally weighted scatterplot smoothing, and the marks on the line show the density of the data (the larger the marks, the more data).

The vasodilator-only and inotrope-only groups were further categorized according to early and late treatment (Table III): 68% of patients on vasodilators and 51% of patients on inotropes received corresponding treatments within 6 hours of admission. For vasodilator-only treated patients, a higher proportion of patients who received early treatment had evidence of pulmonary congestion compared with those who received late treatment. Blood urea nitrogen was slightly higher and systolic blood pressure was slightly lower in patients who received late vasodilator treatment. Among patients who only received inotropes, systolic blood pres-

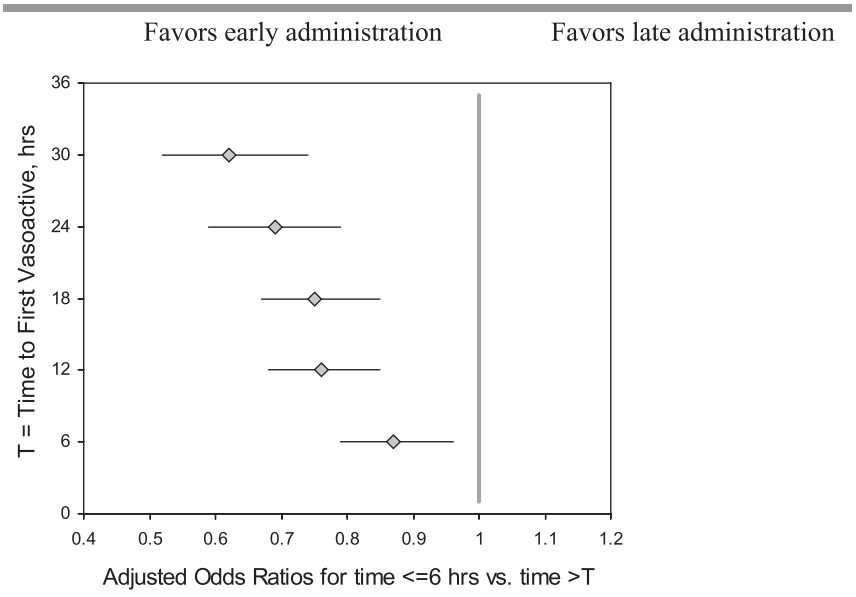

Figure 2. Mortality by time to first vasoactive agent: ≤6 hours vs other time points. Adjusted odds ratios and corresponding 95% confidence intervals for comparison of patient cases receiving vasoactives in the first 6 hours (n=22,178) to patients receiving them after 6 (n=12,582), 12 (n=7207), 18 (n=5324), 24 (n=3445), or 30 (n=1874) hours. The point estimates and 95% confidence intervals shown correspond to the time points on the y-axis. Adjusted for age, systolic blood pressure, diastolic blood pressure, blood urea nitrogen, creatinine, sodium, pulse, and dyspnea at rest.

sure was lower for those who received early administration compared with late administration. Non-IV medications administered and procedures performed during the hospitalization for patients receiving vasodilators or inotropes by time to treatment are displayed in Table IV. Patients who received early vasodilator treatment were less likely to receive in-hospital digoxin or diuretics. Patients who received early inotrope therapy were less likely to receive in-hospital β-blockers. Early administration was associated with an increased rate of mechanical ventilation for both vasodilators and inotropes (Table IV).

In the unadjusted analysis, early administration of vasodilators, but not inotropes, was associated with a lower rate of in-hospital mortality compared with late therapy (Table V). After adjusting for known prognostic factors, there was no statistically significant mortality difference between early (≤6 hours) vasodilator administration and late vasodilator administration (6–48 hours): OR, 0.90; 95% CI, 0.74–1.10. As the time to vasodilator initiation increased, the adjusted mortality OR of early vs late treatment administration decreased from 0.90 (at 6 hours) to 0.66 (at 30 hours), indicating potential benefit of early vasodilator initiation (Figure 3A). However, the results were of borderline significance: P=.015 at 12 hours, P=.033 at 18 hours, P=.13 at 24 hours, and P=.037 at 30 hours. The adjusted mortality OR of early (≤6 hours) vs late inotrope administration decreased from 0.82 (at 6 hours) to 0.62 (at 30 hours), with significant differences between early and late treatment being observed at all time points (Figure 3B).

A higher proportion of patients who received early vasodilator therapy were asymptomatic at discharge, compared with those who received late treatment (56.3% vs 50.3%; P<.0001). No difference was observed in discharge symptoms among inotrope-treated patients according to the time of therapy administration.

Discussion

Administration of vasoactive agents within 6 hours of an ADHF presentation was associated with greater survival, shorter length of stay, and fewer symptoms compared with later administration in this analysis of more than 35,000 hospital admission episodes in the ADHERE database. Most clinical trials testing acute therapies in ADHF have enrolled patients later than 6 hours after admission.[2,12–17] Early administration may result in improved patient outcomes.[2,18] These observational data are hypothesis-generating and suggest productive avenues for further investigation.

Several pathophysiologic arguments support early administration of vasoactive therapies. First, studies of the Chronicle Implantable Hemodynamic Monitoring system (Medtronic, Minneapolis, MN) demonstrate that filling pressures are elevated at the time of presentation in patients with worsening heart failure, and they have often been elevated for several days.[6] Elevated ventricular filling pressures and increased systemic vascular resistance often combined with relatively low cardiac output may worsen the ADHF state by causing subendomyocardial ischemia or renal hypoperfusion leading to functional impairment.[4] Vasoactive agents given early in the course of ADHF may minimize or prevent the consequences of altered hemodynamics. Second, as shown by Johnson and colleagues,[19] hemodynamic improvement is associated with rapid reduction of deleterious neurohormonal activation. Third, the improvement in hemodynamics and dyspnea associated with vasoactive agents may facilitate management of ADHF patients with lower doses of IV loop diuretics. High diuretic doses may cause worsening renal function and have been associated with worse outcomes.[20,21] Patients in whom vasoactive therapy is delayed may often receive "aggressive diuresis" before vasoactive agents are initiated. At the time vasoactive therapies are initiated, blood pressure may be lower and renal function may have worsened as a result of diuretic therapy. These patients may be more likely to experience adverse effects related to vasoactive therapy because of their blood pressure or renal status. Early vasoactive initiation may minimize this concern.

Table III. Baseline Demographics and Clinical Characteristics by Type of Vasoactive Agent

Variable	Vasodilators Only: Early Administration (≤6 hours) N=15,578	Vasodilators Only: Late Administration (6–48 hours) N=7266	*P* Value	Inotropes Only: Early Administration (≤6 hours) N=4106	Inotropes Only: Late Administration (6–48 hours) N=3898	*P* Value
Demographics						
Mean age, y	70.9±14	70.9±14.1	.8430	69.3±14.2	70.4±13.9	.0004
Male	7699 (49.4)	3976 (54.7)	<.0001	2603 (63.4)	2434 (62.4)	.3777
Caucasian	10,897 (72)	5279 (74.5)	.0001	3125 (79.6)	2855 (76)	.0001
Medical history						
Atrial fibrillation	4385 (28.1)	2384 (32.8)	<.0001	1545 (37.6)	1438 (36.9)	.4954
Coronary artery disease	9707 (62.3)	4683 (64.5)	.0019	2665 (64.9)	2568 (65.9)	.3595
COPD/asthma	4851 (31.1)	2272 (31.3)	.8448	1178 (28.7)	1228 (31.5)	.0061
Chronic dialysis	814 (5.2)	184 (2.5)	<.0001	104 (2.5)	116 (3.0)	.2256
Chronic renal insufficiency	5071 (32.6)	2650 (36.5)	<.0001	1595 (38.8)	1555 (39.9)	.338
Diabetes	7324 (47)	3535 (48.7)	.0211	1629 (39.7)	1683 (43.2)	.0015
Heart failure history	12,121 (77.8)	5893 (81.1)	<.0001	3726 (90.7)	3404 (87.3)	<.0001
Hyperlipidemia	6294 (40.4)	2991 (41.2)	.2753	1494 (36.4)	1383 (35.5)	.3985
Hypertension	12,328 (79.1)	5525 (76)	<.0001	2405 (58.6)	2475 (63.5)	<.0001
Prior myocardial infarction	5095 (35.8)	2481 (36.1)	.6075	1506 (41.8)	1371 (39.7)	.0719
Prior stroke	2623 (16.8)	1197 (16.5)	.4925	608 (14.8)	564 (14.5)	.6684
Prior ventricular tachycardia/fibrillation	1466 (9.4)	859 (11.8)	<.0001	963 (23.5)	749 (19.2)	<.0001
Signs and symptoms						
Admission to the emergency department	12,568 (80.7)	5797 (79.8)	.1083	1918 (46.7)	2710 (69.5)	<.0001
Congestion on first chest radiograph	11,787 (82.1)	5093 (75.7)	<.0001	2340 (68.5)	2461 (70.5)	.0637
Dyspnea at rest	6791 (43.6)	2571 (35.4)	<.0001	1570 (38.2)	1299 (33.3)	<.0001
Edema	10,368 (66.6)	5183 (71.3)	<.0001	2670 (65)	2654 (68.1)	.0037
Fatigue	4336 (27.8)	2344 (32.3)	<.0001	1771 (43.1)	1538 (39.5)	.0008
Rales	11,612 (74.5)	4997 (68.8)	<.0001	2512 (61.2)	2549 (65.4)	.0001
Laboratory data and vital signs						
LVEF, %	37.2±16.6	34.2±16.5	<.0001	26.9±15.3	27.7±15.1	.0388
BUN, mg/dL	31.2±19.8	34.6±21.8	<.0001	44.3±28	42.6±26.6	.0053
Serum creatinine, mg/dL median (IQR)	1.4 (1.1–1.9)	1.5 (1.1–2)	<.0001	1.6 (1.2–2.3)	1.6 (1.2–2.3)	.4042
Sodium, mmol/L	138.4±4.4	137.9±4.6	<.0001	136.2±5.4	136.5±5.2	<.0001
BNP, pg/mL median (IQR)	991 (517–1670)	1146 (626–1960)	<.0001	1060 (520–1440)	1170 (612–1740)	.0001
Systolic blood pressure, mm Hg	159.5±39.1	143.4±32.8	<.0001	114.5±28.1	122.1±27.3	<.0001
Heart rate, beats/min	92.4±23.4	86.5±21.2	<.0001	84.7±21.4	86.6±21.6	.0001
Pre-admission medications						
ACE inhibitor	6606 (42.4)	3071 (42.3)	.8239	1920 (46.8)	1700 (43.6)	.005
Angiotensin receptor blocker	2159 (13.9)	987 (13.6)	.5666	530 (12.9)	521 (13.4)	.5383
β-Blocker	9079 (58.3)	4335 (59.7)	.0519	2179 (53.1)	2111 (54.2)	.317
Digoxin	3920 (25.2)	2209 (30.4)	<.0001	1831 (44.6)	1568 (40.3)	.0001
Diuretic	10,895 (70)	5646 (77.7)	<.0001	3487 (84.9)	3209 (82.4)	.002

Abbreviations: ACE, angiotensin-converting enzyme; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; LVEF, left ventricular ejection fraction. Continuous variables are reported as mean ± SD unless otherwise indicated. Categoric variables are reported as No. (%). To convert to SI units, multiply SCr × 88.4 (for μmol/L); multiply BUN × 0.357 (for mmol/L); multiply sodium × 1.0 (for mmol/L).

Identifying new effective therapies for ADHF has been challenging. Currently, no acute management modality has been shown to improve 30-day mortality in the hospitalized population. Late administration may be one reason that improvements in clinical outcomes have not been observed with vasoactive therapy. Most clinical trials testing vasoactive agents have enrolled patients from 24 to 72 hours after hospital admission. In this analysis, the mortality risk reduction for early administration (≤6 hours) was greater as the time between presentation and vasoactive administration increased. For example, the adjusted OR for mortality was 0.69 (95% CI, 0.59–0.79; $P<.001$) when early administration was compared with administration that occurred >24 hours after presentation (Figure 2). This observation is hypothesis-generating and suggests that the delay in vasoactive therapy administration that has occurred in the majority of clinical trials may have prevented the detection of a beneficial effect on outcomes.

Table IV. Procedures and Medications During the Hospitalization by Type of Vasoactive Agent

Variable	Vasodilators Only: Early Administration (≤6 hours) N=15,578	Vasodilators Only: Late Administration (6–48 hours) N=7266	*P* Value	Inotropes Only: Early Administration (≤6 hours) N=4106	Inotropes Only: Late Administration (6–48 hours) N=3898	*P* Value
Non-IV medications during hospitalization						
ACE inhibitor	9372 (60.2)	4206 (57.9)	.0011	2002 (48.8)	2012 (51.6)	.0106
Angiotensin receptor blocker	2490 (16.0)	1161 (16.0)	.9933	535 (13.0)	553 (14.2)	.1311
β-Blocker	11,258 (72.3)	5389 (74.2)	.0026	2262 (55.1)	2369 (60.8)	<.0001
Digoxin	5101 (32.7)	2853 (39.3)	<.0001	2069 (50.4)	1930 (49.5)	.4328
Diuretic	11,657 (74.8)	5772 (79.4)	<.0001	3213 (78.3)	3073 (78.8)	.5248
Procedures during hospitalization						
Cardiopulmonary resuscitation	113 (0.7)	54 (0.7)	.883	160 (3.9)	172 (4.4)	.2474
Cardiac catheterization	1787 (11.5)	838 (11.5)	.8914	384 (9.4)	336 (8.6)	.2524
Defibrillation	66 (0.4)	50 (0.7)	.0088	100 (2.4)	87 (2.2)	.5468
Mechanical ventilation	858 (5.5)	248 (3.4)	<.0001	524 (12.8)	427 (11)	.0125
Dialysis initiated during hospitalization	213 (1.4)	133 (1.8)	.0076	87 (2.1)	111 (2.8)	.0359
Ultrafiltration	277 (2.4)	91 (1.6)	.0002	34 (1.4)	56 (2.5)	.0129

Abbreviations: ACE, angiotensin-converting enzyme; IV, intravenous. Categoric variables are reported as No. (%).

Table V. Clinical Outcomes by Early or Late Administration by Type of Vasoactive Agent

Variable	Vasodilators Only: Early Administration N=15,578	Vasodilators Only: Late Administration N=7266	*P* Value	Inotropes Only: Early Administration N=4106	Inotropes Only: Late Administration N=3898	*P* Value
Mortality	291 (1.9)	178 (2.4)	.0039	468 (11.4)	451 (11.6)	.8093
Time in emergency department, h median (IQR)	4.6 (3.2–6.6)	5.5 (3.9–7.8)	<.0001	4.1 (2.9–5.8)	5.2 (3.6–7.3)	<.0001
In-hospital length of stay, d median (IQR)	3.9 (2.6–6.1)	4.8 (3.1–7.3)	<.0001	5.4 (3.2–9)	5.9 (3.8–9.6)	<.0001
Total length of stay, d median (IQR)	4.1 (2.8–6.3)	5 (3.4–7.5)	<.0001	5.6 (3.3–9)	6.1 (4–9.8)	<.0001
Admitted to ICU	5148 (33)	1578 (21.7)	<.0001	1686 (41.1)	1339 (34.4)	<.0001
ICU time, d median (IQR)	2 (1.1–3.1)	2.5 (1.5–4.3)	<.0001	3 (1.7–5.3)	3.3 (1.9–5.8)	.0036
Asymptomatic at discharge	7712 (56.3)	3199 (50.3)	<.0001	1333 (41.9)	1299 (42.9)	.4165

Abbreviations: ICU, intensive care unit; IQR, interquartile range; Continuous variables are reported as median (IQR). Categoric variables are reported as No. (%).

The adjusted mortality reduction associated with early administration was consistent when vasodilators and inotropes were examined separately. Statistical significance was not uniformly achieved for comparisons between early and late vasodilator treatment. This finding may have been due to the heterogeneous nature of the vasodilator group. Despite this, the adjusted point estimates were consistently in favor of early administration for both vasodilators and inotropes compared with later administration. Consistent with the report by Abraham and associates,[11] mortality was lower in patients treated with vasodilators compared with inotropes, even after adjustment for systolic blood pressure and other variables. The observation that inotropes were associated with a high initial mortality that subsequently declined may be related to earlier inotrope use in severely ill patients, such as those in obvious cardiogenic shock. It is possible that this may account for the observed high mortality among inotrope-treated patients in the first several hours, but we cannot definitively draw this conclusion from these data.

Patients treated with vasoactive agents had somewhat higher ICU admission rates. This observation could have been related to institutional policies requiring patients treated with vasoactive agents to be admitted to the ICU.

Although several statistically significant differences in baseline characteristics were present between the early and late administration groups, the absolute differences were often small and of questionable clinical relevance; however, they reached statistical significance because of the large number of observations in the database. Early vasoactive therapy was associated with a lower mortality compared with late administration after adjusting for prognostic factors, suggesting that this

observation was not likely due to an imbalance in severity of illness between groups.

Several limitations should be considered when evaluating these data. Data were collected by medical chart review and were dependent upon the accuracy and completeness of documentation and abstraction. Factors that were not collected in the database may have been present and could have influenced the findings. Because this study was not a prospective controlled trial, we can only report the association between timing of vasoactive therapy administration and outcomes. Causality cannot be assessed from these data. The ADHERE Registry accumulates data on individual hospitalizations, not on individual patients. However, each hospitalization episode represents a unique opportunity to either survive or not survive.

In conclusion, compared to early administration, late vasoactive treatment was associated with increased mortality in patients hospitalized with ADHF. These provocative observational data suggest that early administration may be necessary to realize the potential benefits of vasoactive therapy in ADHF patients. Prospective randomized studies should be designed to further evaluate the role of early vasoactive administration in this population.

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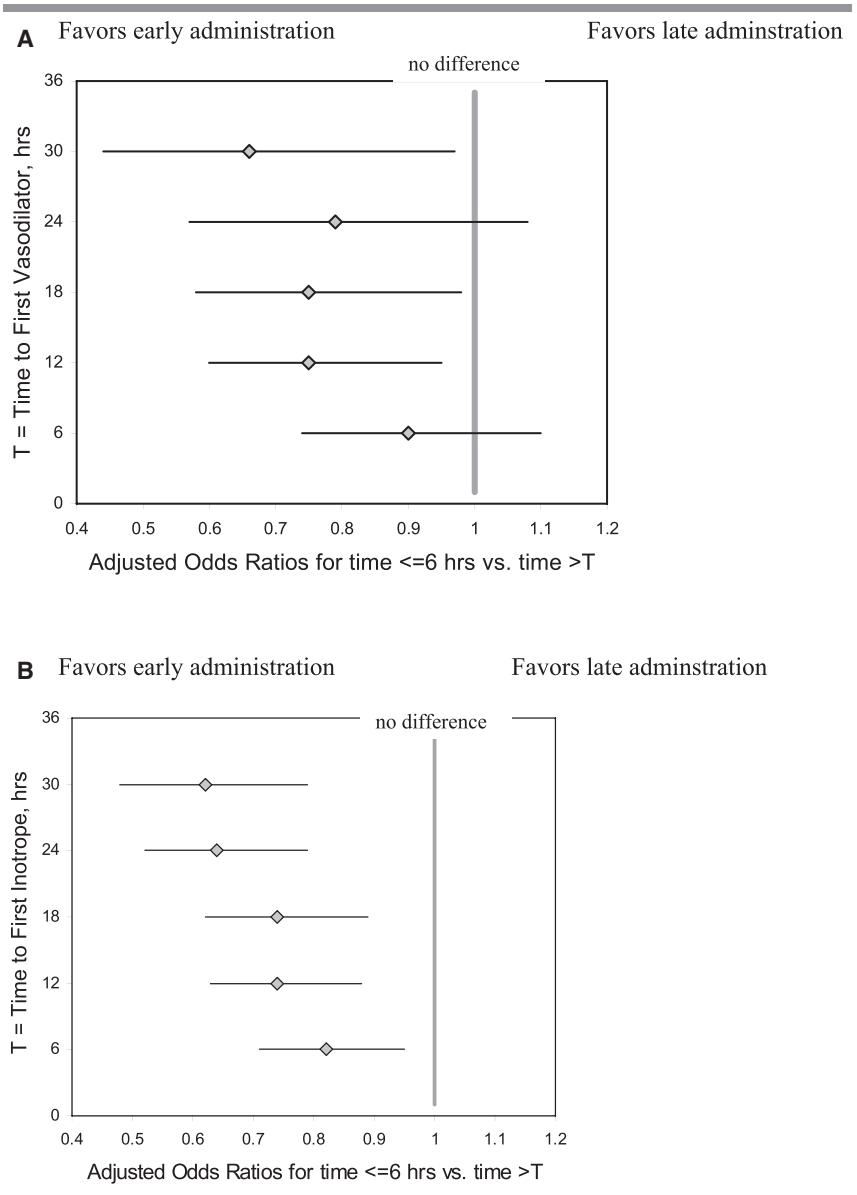

Figure 3. (A) Mortality by time to first vasodilator: ≤6 hours vs other time points. Adjusted odds ratios and corresponding 95% confidence intervals (CIs) for comparison of patient cases receiving vasodilators in the first 6 hours (n=15,281) to patients receiving them after 6 (n=7114), 12 (n=3763), 18 (n=2699), 24 (n=1695), or 30 (n=855) hours. The point estimates and 95% CIs shown correspond to the time points on the y-axis. (B) Mortality by time to first inotrope: ≤6 hours vs other time points. Adjusted odds ratios and corresponding 95% CIs for comparison of patient cases receiving inotropes in the first 6 hours (n=3890) to patients receiving them after 6 (n=3772), 12 (n=2471), 18 (n=1911), 24 (n=1281), or 30 (n=759) hours. The point estimates and 95% CIs shown correspond to the time points on the y-axis. Adjusted for age, systolic blood pressure, diastolic blood pressure, blood urea nitrogen, creatinine, sodium, pulse, and dyspnea at rest.

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