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Timing of Immunoreactive B-Type Natriuretic Peptide Levels and Treatment Delay in Acute Decompensated Heart Failure

An ADHERE (Acute Decompensated Heart Failure National Registry) Analysis

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Objectives We undertook this analysis to determine whether there is a relationship between the time to measurement of immunoreactive B-type natriuretic peptide (iBNP) and early intervention for acutely decompensated heart failure (ADHF) and whether these variables are associated with morbidity and mortality in ADHF patients.

Background Although natriuretic peptides (NPs) can aid emergency department (ED) physicians in the diagnosis of ADHF, the relationship between the time to measurement of NP levels and time to treatment is not clear. In addition, the impact of time to treatment on clinical outcomes has not been demonstrated.

Methods Patients from ADHERE (Acute Decompensated Heart Failure National Registry) who were admitted to the ED and who received intravenous diuretics were included. Recordings of iBNP levels and the timing of intravenous diuretic therapy were documented. Patients were divided by quartiles of time to treatment and iBNP levels, creating 16 categories.

Results In 58,465 ADHF episodes from 209 hospitals, patients with the longest average time to iBNP draw also had the longest time to treatment. Mean ED time increased with increased time-to-treatment quartiles. Rales on initial examination were associated with early recognition of HF and earlier institution of therapy. The later the treatment took place, the fewer patients were asymptomatic at the time of hospital discharge. Within the time-to-treatment quartiles, mortality increased with increasing iBNP. Treatment delay was independently, but modestly, associated with increased in-hospital mortality with a risk-adjusted odds ratio 1.021, 95% confidence interval 1.010 to 1.033, and $p < 0.0001$, per every 4-h delay.

Conclusions In the ED setting, delayed measurement of iBNP levels and delay in treatment for ADHF were strongly associated. These delays were linked with modestly increased in-hospital mortality, independent of other prognostic variables. The adverse impact of delay was most notable in patients with greater iBNP levels (Registry for Acute Decompensated Heart Failure Patients; NCT00366639). (J Am Coll Cardiol 2008;52:534–40) © 2008 by the American College of Cardiology Foundation

Acute decompensated heart failure (ADHF) occurs frequently, accounting for more than 1 million hospitalizations annually in the U.S. (1). Prompt and accurate diagnosis of heart failure (HF) in the emergency department (ED) is a necessary first step for insuring that early and appropriate therapy is given. Previous work has suggested that delayed therapy may be associated with increased length of stay and mortality (2–4). A better understanding of the complex process of timely diagnosis and treatment may help to improve patient care.

A substantial body of prospective, randomized trial data has demonstrated that laboratory testing for immunoreactive B-type natriuretic peptide (iBNP) levels represents a useful and cost-effective adjunct for the diagnosis of HF in the undifferentiated patient presenting with shortness of

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breath (5). Even when a high pretest likelihood of heart failure based on the clinical presentation is present, the measurement of iBNP gives added important prognostic information that might help drive triage and treatment decisions.

Although natriuretic peptide (NP) (i.e., B-type natriuretic peptide [BNP] and N-terminal pro-B-type natriuretic peptide) levels clearly aid in the ED diagnosis of HF (5,6), it is unknown whether there is a relationship between the time to NP levels and initiation of treatment in patients with suspected ADHF. Furthermore, it is unknown whether the timing of obtaining NP levels influences clinical outcomes in this setting. The purpose of this analysis is to determine whether there is a relationship between the time to measurement of iBNP and time to initial treatment and whether these variables are associated with morbidity and mortality among patients presenting with ADHF.

Methods

This analysis was performed with ADHERE (Acute Decompensated Heart Failure National Registry). This registry collected detailed patient hospitalization data from initial presentation in the hospital or ED until discharge, transfer, or in-hospital death (7,8). The registry contains data on patients hospitalized with acute decompensated HF in community, tertiary, and academic centers from all regions of the country (8). For the purpose of the registry, ADHF was defined as new-onset decompensated HF or decompensation of chronic, established HF with symptoms sufficient to warrant hospitalization. The design, methods, and patient characteristics in the ADHERE registry have been described previously (7).

In brief, medical records were reviewed at participating study sites, and data from consecutive eligible male and female patients >18 years of age at the time of hospitalization were entered in the registry with an electronic case report form incorporating real-time validity checking (7,8). These data included demographic information, medical history, baseline clinical characteristics, initial evaluation, treatment received, procedures performed, hospital course, and patient disposition. Standardized definitions were used for all patient-related variables, clinical diagnoses, and hospital outcomes.

Importantly, registry participation did not require any alteration of treatment or hospital care, and entry of data into the registry was not contingent on the use of any particular therapeutic agent or treatment. Institutional review board approval was required for all participating centers; however, informed consent of individuals was not required for registry entry. To preserve patient confidentiality, direct patient identifiers were not collected, and data are reported only in aggregate format. Therefore, registry entries reflect individual hospitalization episodes, not individual patients, and multiple hospitalizations of the same patient occur as separate records.

Abbreviations and Acronyms

ADHERE = Acute Decompensated Heart Failure National Registry
ADHF = acute decompensated heart failure
CI = confidence interval
ED = emergency department
GEE = generalized estimating equation
HF = heart failure
iBNP = immunoreactive B-type natriuretic peptide
ICU = intensive care unit

In the beginning of 2003, the ADHERE registry hospitals began to use expanded range BNP testing (range 0 to 5,000 pg/ml). In this current study, we analyzed the ADHERE registry data from April 2003 through May 2006. There were 187,575 records entered in the ADHERE registry from inception, and 95,898 (51%) patient episodes had iBNP levels obtained. There were 37,433 records that were excluded from this analysis because ED was not the initial point of care, the records were missing time to intravenous diuretics or time to iBNP being drawn, or the hospitalization occurred before the extended range iBNP assay was widely available. Data from 209 sites were used for this analysis.

Study population. For this analysis, only patients admitted to the emergency department, receiving intravenous (IV) diuretics and having an iBNP level recorded were included. Inclusion criteria also required that the timing of IV diuretic therapy was documented. Previous ADHERE registry analyses have shown that parenteral loop-blocking diuretics are the first pharmacologic intervention in ADHF treatment in more than 90% of patients treated for ADHF. Time to treatment was defined as the time from ED admission to first use of IV diuretic. Time to treatment and iBNP levels being drawn were divided into quartiles, creating 16 possible patient subgroups.

Statistical analyses. By using univariate analysis, we compared demographic, therapeutic, and outcome variables across quartiles of time-to-treatment administration for the total population and within each iBNP quartile. The hypothesis of no differences in patients' characteristics and outcomes was tested with the chi-square, analysis of variance, and Kruskal-Wallis tests, as appropriate. Kruskal-Wallis testing was used to analyze outcome variables with skewed distribution. Two-sided p values were reported. A total of 1.2% of records were excluded for 1 or more missing values. With the large sample size, statistical significance with small differences in clinical variables was expected.

Multivariable modeling was performed for time to BNP and time to IV diuretics in relation to in-hospital mortality risk. The models included variables previously demonstrated to have the greatest prognostic value in the ADHERE registry (8). The adjusted model includes covariates for age, blood urea nitrogen, systolic blood pressure, diastolic blood pressure, creatinine, sodium, heart rate, and dyspnea at rest. Generalized estimating equations (GEE) models were used to adjust for the correlation of data within hospitals. An additional model was developed to determine hospital and patient characteristics that were predictive of time to BNP levels of 2 or

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more hours. All variables that were univariate predictors for this outcome were entered into the model. Both forward and backward selection yielded similar variables. These analyses were performed using version 8.2 of SAS software (SAS Institute, Cary, North Carolina).

Results

There were 187,575 records entered in the ADHERE registry from inception. During this time 95,898 (51%) patient episodes had iBNP levels obtained. An additional 37,433 records were excluded from this analysis because ED was not the initial point of care, the records were missing time to intravenous diuretics or time to iBNP, or the hospitalization occurred before the extended range iBNP assay was widely available (before April 2003). This study included 58,465 ADHF episodes from 209 hospitals.

Table 1 shows the patients' demographic, clinical, and laboratory variables by quartile of door-to-treatment time.

Table 1 Characteristics of Patient Cohorts Divided by Time to Treatment With Intravenous Diuretics

	Quartile of Time to Diuretic Treatment					
Characteristic	Q1 ≤1.05 (n = 14,785)	Q2 1.05–2.27 (n = 14,475)	Q3 2.28–4.98 (n = 14,560)	Q4 >4.98 (n = 14,645)	All (n = 58,465)	p Value
Age, Q1 [median] Q3	65.3 [76.1] 83.6	65.2 [76.5] 84.0	65.5 [77.1] 84.3	65.1 [76.5] 83.8	65.3 [76.5] 83.9	0.0033*
Gender (male), n/total (%)	6,967/14,780 (47.1)	6,848/14,473 (47.3)	6,738/14,558 (46.3)	6,896/14,641 (47.1)	27,449/58,452 (47.0)	0.2943†
Black race, n/total (%)	2,631/14,277 (18.4)	2,711/13,941 (19.4)	2,692/14,032 (19.2)	2,883/14,152 (20.4)	10,917/56,402 (19.4)	0.0005†
White race, n/total (%)	10,918/14,277 (76.5)	10,470/13,941 (75.1)	10,492/14,032 (74.8)	10,444/14,152 (73.8)	42,324/56,402 (75.0)	<0.0001†
Past medical history						
Atrial fibrillation, n/total (%)	4,383/14,785 (29.6)	4,627/14,475 (32.0)	4,752/14,560 (32.6)	4,743/14,645 (32.4)	18,505/58,465 (31.7)	<0.0001†
Coronary artery disease, n/total (%)	9,076/14,785 (61.4)	8,499/14,475 (58.7)	8,345/14,560 (57.3)	8,414/14,645 (57.5)	34,334/58,465 (58.7)	<0.0001†
Renal insufficiency, n/total (%)	4,500/14,785 (30.4)	4,151/14,475 (28.7)	4,006/14,560 (27.5)	4,234/14,645 (28.9)	16,891/58,465 (28.9)	<0.0001†
Dialysis, n/total (%)	476/14,785 (3.2)	309/14,474 (2.1)	309/14,560 (2.1)	310/14,645 (2.1)	1404/58,464 (2.4)	<0.0001†
Current smoker, n/total (%)	2,042/13,776 (14.8)	1,969/13,481 (14.6)	1,861/13,462 (13.8)	1,901/13,457 (14.1)	7,773/54,176 (14.3)	0.0785†
HF history, n/total (%)	11,528/14,785 (78.0)	11,028/14,475 (76.2)	10,675/14,560 (73.3)	11,030/14,645 (75.3)	44,261/58,465 (75.7)	<0.0001†
Initial evaluation						
Edema, n/total (%)	10,000/14,785 (67.6)	9,860/14,475 (68.1)	9,370/14,560 (64.4)	9,138/14,645 (62.4)	38,368/58,465 (65.6)	<0.0001†
Rales, n/total (%)	11,726/14,785 (79.3)	10,656/14,475 (73.6)	9,928/14,560 (68.2)	9,197/14,645 (62.8)	41,507/58,465 (71.0)	<0.0001†
First chest X-ray with congestion, n/total (%)	12,144/14,417 (84.2)	11,075/14,062 (78.8)	10,620/14,127 (75.2)	9,871/14,051 (70.3)	43,710/56,657 (77.1)	<0.0001†
BUN (mg/dl), Q1 [median] Q3	18.0 [25.0] 38.0	18.0 [25.0] 38.0	17.0 [25.0] 38.0	17.0 [26.0] 40.0	17.0 [25.0] 38.0	<0.0001*
Creatinine (mg/dl), Q1 [median] Q3	1.0 [1.3] 1.8	1.0 [1.3] 1.8	1.0 [1.3] 1.8	1.0 [1.3] 1.8	1.0 [1.3] 1.8	<0.0001*
Systolic blood pressure (mm Hg), Q1 [median] Q3	129.0 [150.0] 177.0	123.0 [144.0] 166.0	121.0 [141.0] 162.0	118.0 [138.0] 160.0	122.0 [143.0] 166.0	<0.0001*
iBNP level (pg/ml), Q1 [median] Q3	455.1 [848.0] 1,661.0	467.0 [887.0] 1,738.0	473.0 [913.0] 1,778.5	416.0 [799.0] 1,630.0	453.0 [861.0] 1,700.0	<0.0001*
Time to iBNP level (h), Q1 [median] Q3	0.3 [0.6] 1.0	0.5 [0.8] 1.4	0.7 [1.1] 2.0	0.6 [1.3] 3.9	0.5 [0.9] 1.8	
Mean (SD)	2.9 (12.4)	2.7 (11.3)	3.2 (11.0)	6.8 (23.2)	4.8 (14.6)	<0.0001‡
Hospitalization						
Time in ED (h), Q1 [median] Q3	2.8 [4.0] 5.8	3.5 [4.8] 6.5	4.2 [5.5] 7.3	4.2 [6.0] 8.4	3.6 [5.0] 7.0	<0.0001‡
Vasoactive treatment, n/total (%)	5,699/14,785 (38.5)	3,994/14,475 (27.6)	3,503/14,560 (24.1)	4,180/14,645 (28.5)	17,376/58,465 (29.7)	<0.0001†
Hospital length of stay, Q1 [median] Q3	2.6 [4.0] 6.7	2.6 [3.9] 6.4	2.6 [3.9] 6.5	2.8 [4.5] 7.1	2.6 [4.0] 6.7	<0.0001‡
ICU length of stay, Q1 [median] Q3	1.2 [2.2] 3.9	1.2 [2.3] 4.0	1.3 [2.5] 4.5	1.4 [2.8] 4.8	1.3 [2.3] 4.2	<0.0001‡
Mortality, n/total (%)	535/14,785 (3.6)	470/14,475 (3.2)	453/14,560 (3.1)	583/14,645 (4.0)	2,041/58,465 (3.5)	0.0002†

p values for continuous variables are from a *1-way analysis of variance, a †chi-square for categorical variables, or ‡Wilcoxon test.
BUN = blood urea nitrogen; ED = emergency department; HF = heart failure; iBNP = immunoreactive B-type natriuretic peptide; ICU = intensive care unit.

There were no differences in time to treatment with respect to gender. In multivariate analysis, patients with a history of chronic obstructive pulmonary disease or previous heart failure, and those with rales, congestion on chest X-ray, or dyspnea at rest received therapy earlier. On average, 79% of patients in the first quartile of time to treatment had rales, compared with 63% for the fourth quartile ($p < 0.001$). The percent of patients with rales also increased with increasing BNP quartiles from an average of 67% for iBNP <449 pg/ml to 74% for the group with BNP levels >1,738 pg/ml ($p < 0.001$). The presence of rales on initial examination was associated with early recognition of heart failure and, hence, earlier institution of therapy.

Interestingly, greater iBNP levels and rales on initial examination were closely associated. The multivariate data demonstrated treatment delays in African Americans and slight delays in older patients. There were 23% of patients who had iBNP levels obtained 2 or more hours after presentation. On multivariate analysis, treatment in an academic hospital, western and northeastern region, and history of stroke were associated with longer time to iBNP measurement (Table 2).

Figure 1 shows the relationship of the time iBNP level was drawn and time to treatment. Patients with the longest time to iBNP draw also had the longest time to treatment. This relationship between time to treatment and time to iBNP level was maintained throughout each quartile of BNP level (Fig. 2).

Figure 3 shows the average time spent in the ED by the patient in hours by quartiles of time to treatment and iBNP level. Mean ED time increased with increased time-to-treatment quartiles. Once again, this relationship was maintained throughout all quartiles of iBNP.

Figure 4 demonstrates the downstream effects of delayed treatment of ADHF. The later the treatment took place, the fewer proportion of patients were asymptomatic at the time of discharge. Of note, within each quartile of treatment time, the greater the BNP level, the lower percentage of patients who were asymptomatic at discharge.

Figure 5 shows unadjusted in hospital mortality data for each of the 16 time-to-treatment and iBNP subgroups. Within most time-to-treatment quartiles, mortality increases with increasing iBNP. However, patients with low iBNP who received very early treatment constitute an exception in that they experienced relatively greater mortality. This observation probably has a complex multifactorial explanation, as discussed herein. Within the 2 lower iBNP quartiles, the mortality rate is essentially unchanged between the <1.05- and >4.98-h time-to-treatment groups. However, in the third-highest and the highest quartiles of iBNP, treatment delays associated with average increased mortality from 3.7% to 4.1% and from 5.5% to 7.3%,

Table 2 Hospital and Patient Characteristics Predictive of Delays in iBNP Testing

Characteristic	Adjusted Odds Ratio	95% Confidence Intervals
Academic	1.453	1.370–1.540
Region		
West vs. Mid-Atlantic	1.226	1.099–1.367
South vs. Mid-Atlantic	0.987	0.913–1.067
Northeast vs. Mid-Atlantic	1.877	1.679–2.099
Midwest vs. Mid-Atlantic	0.613	0.566–0.665
Previous heart failure history	0.869	0.814–0.927
Stroke	1.078	1.003–1.159
COPD	0.938	0.884–0.997
Beta-blocker use before admission	0.887	0.838–0.939
Dyspnea at rest	0.761	0.718–0.808
Congestion on examination	0.832	0.780–0.887
Rales	0.841	0.780–0.893
Pulse	0.999	0.997–1.000
Diastolic blood pressure	0.995	0.993–0.996
QRS duration on ECG	0.999	0.998–0.999

COPD = chronic obstructive pulmonary disease; ECG = electrocardiogram; iBNP = immunoreactive B-type natriuretic peptide.

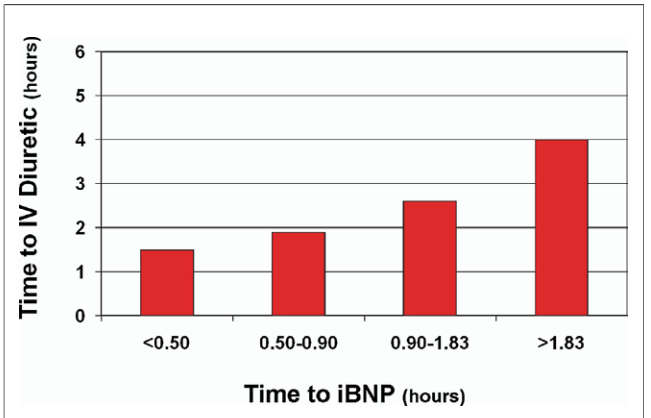

Figure 1 Time to iBNP Versus Time to Treatment

The relationship between median time to iBNP drawn by quartiles and median time to initial intravenous diuretic treatment is shown. iBNP = immunoreactive B-type natriuretic peptide; IV = intravenous.

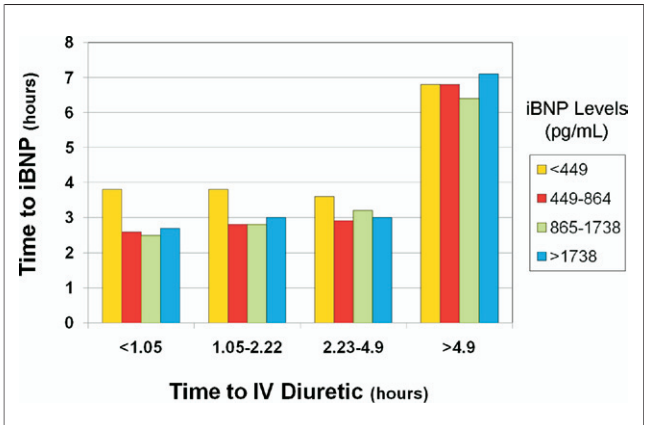

Figure 2 Time to iBNP Versus Time to Treatment by iBNP Quartile

The plot shows the relationship between mean time to iBNP level being drawn and time to initial intravenous diuretic treatment for patients in each iBNP quartile. iBNP = immunoreactive B-type natriuretic peptide; IV = intravenous.

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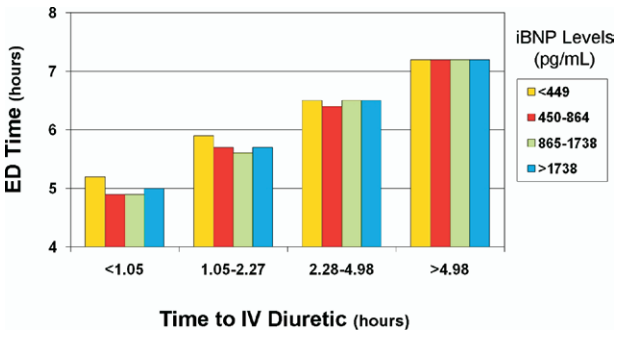

Figure 3 ED Time Versus Quartiles of Time to Diuretic by iBNP levels

The relationship between time to initial diuretic treatment and total time spent in the emergency department (ED), divided into quartiles, is shown. Each quartile of time to treatment is divided by quartiles of iBNP levels. iBNP = immunoreactive B-type natriuretic peptide; IV = intravenous.

respectively, which represents a relative increase in mortality of 11% and 32%. After multivariable analysis, the increased mortality in the highest iBNP quartile with treatment delays remained statistically significant.

On multivariable GEE modeling accounting for the correlation of data within hospitals, longer time to BNP as a continuous variable was a modest predictor of increased in-hospital mortality, independent of other predictive variables, with odds ratio (OR) (per hour) 1.004, 95% confidence intervals (CI): 1.002 to 1.006, and p = 0.0002. Longer time to IV diuretic treatment was also independently associated with a modest increased risk of in-hospital mortality in the GEE model with OR (per hour) 1.004, 95% CI 1.002 to 1.006, and p = 0.0001. The risk-adjusted OR was 1.021, 95% CI: 1.010 to 1.033, and p = 0.0001, per every 4-h delay. Other predictive variables are shown in Table 3.

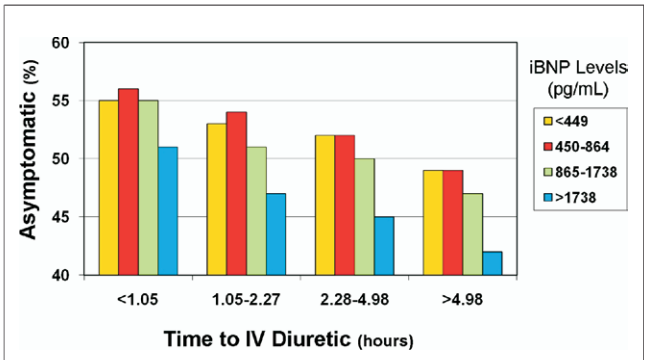

Figure 4 Patients Asymptomatic at Discharge Versus iBNP Levels

The influence of time to initial treatment on the percentage of patients who are asymptomatic at hospital discharge is shown with time to initial diuretic treatment divided into quartiles. Each quartile of time to treatment is divided by quartiles of iBNP levels. iBNP = immunoreactive B-type natriuretic peptide; IV = intravenous.

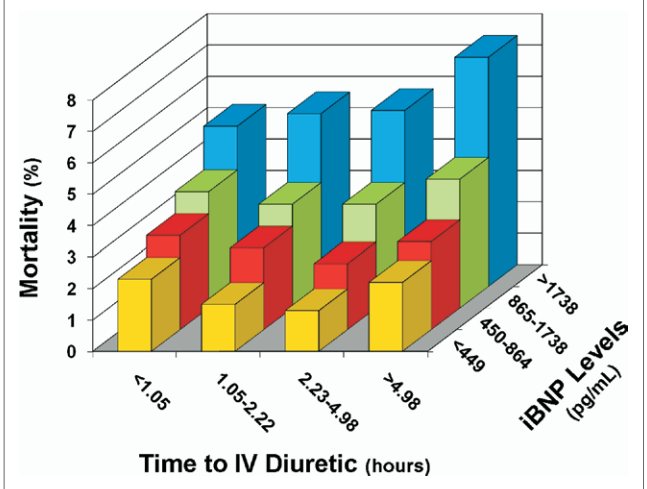

Figure 5 Hospital Mortality, Time to Treatment, and iBNP Level

This 3-dimensional plot shows the relationship of hospital mortality (%) to time of initial treatment (quartiles) and initial iBNP levels being drawn (quartiles). iBNP = immunoreactive B-type natriuretic peptide; IV = intravenous.

Discussion

Previous studies have shown that NP levels in patients presenting with HF are predictive of future outcomes (9–14). In both acute and chronic HF, BNP provides important prognostic information, with every 100 pg/ml increase associated with a 35% increase in the risk of death (15). Our data demonstrate that in patients presenting to the ED with ADHF: 1) a delay in obtaining iBNP levels is associated with prolonged time to treatment; 2) patients with rales on initial examination, and those with a history of coronary artery disease or HF tend to receive earlier treatment; and 3) across a spectrum of time-to-treatment and iBNP levels, both delayed treatment and increased iBNP were modestly associated with increased mortality. These observations remained valid whether the data were analyzed by quartiles or as continuous variables and were independent of other prognostic variables, suggesting that, with every successive delay there may be an increased risk of adverse outcomes.

The data presented suggest that the diagnosis of ADHF was often not made with sufficient certainty to initiate treatment until after the iBNP level was known. Supporting evidence for this hypothesis includes the paucity of physical examination findings, such as rales and edema, the absence of congestion on the chest X-ray, and the absence of a history of HF in the patients who were treated later. The findings of this study suggest that substantial time delay before the iBNP level is obtained in the ED may contribute to delay in initiating ADHF treatment with IV diuretics. Reducing the time from arrival to iBNP blood draw may be appropriate for quality of care improvement efforts.

Several previous investigations have suggested that treatment delays in ADHF are associated with worse outcomes.

Table 3 Variables Predictive of In-Hospital Mortality

Variable	Adjusted Odds Ratio	95% Confidence Intervals	p Values
Time to IV diuretic (per h)	1.004	1.002–1.005	<0.0001
Creatinine (per mg/dl)	1.042	0.996–1.090	0.0743
BUN (per mg/dl)	1.019	1.017–1.022	<0.0001
Systolic blood pressure (per mm Hg)	0.987	0.985–0.989	<0.0001
Diastolic blood pressure (per mm Hg)	0.990	0.987–0.994	<0.0001
Serum sodium (per mEq/l)	0.972	0.963–0.980	<0.0001
Pulse (per beats/min)	1.015	1.013–1.017	<0.0001
Dyspnea at rest	1.509	1.376–1.655	<0.0001
Age (per yr)	1.037	1.033–1.042	<0.0001

BUN = blood urea nitrogen; IV = intravenous.

In a study of 8,000 patients transferred to hospital by ambulance, of which 499 were ultimately diagnosed with ADHF, there was a significant reduction in mortality in those receiving early ADHF therapy compared with those whose therapy was delayed by only 35 min (OR: 2.51, 95% CI: 1.37 to 4.55) (4). Although a mortality benefit was observed in the ADHF cohort, this was at the cost of a markedly increased death rate in the non-ADHF cohort if mistakenly diagnosed and treated for ADHF. In the 106 dyspneic patients ultimately found to not have ADHF, mortality was increased by >300% (from 3.8% to 13.8%, $p < 0.05$) if they received ADHF therapy rather than appropriate treatment. A similar adverse effect of early but inappropriate therapy may be a factor in explaining the high mortality of our earliest treatment/lowest iBNP subgroup.

In an separate ADHERE registry analysis of patients receiving vasoactive infusions (defined as dopamine, dobutamine, milrinone, nesiritide, nitroglycerin, or nitroprusside) for ADHF in the ED, compared with those receiving a vasoactive on the inpatient floor, an association of treatment delay and adverse outcomes was reported (2,3). Patients receiving ED vasoactive agents had a significantly decreased overall length of hospital stay (4.5 vs. 7 days, $p < 0.0001$), intensive care unit (ICU) length of stay (2.0 vs. 3.1 days, $p < 0.0001$), and in-hospital mortality (4.3% vs. 10.9%, $p < 0.0001$). Time-to-BNP levels and absolute BNP values were not recorded in this study.

Results congruent with the aforementioned analyses were reported in another ADHERE registry evaluation of patients treated with nesiritide (16). This study compared patients receiving ED nesiritide to those in whom therapy was delayed until inpatient hospitalization. Early treatment patients had a shorter mean length of hospital stay (5.4 vs. 6.9 days) and, if treated in an ICU, they had shorter ICU length of stay (3.2 vs. 3.7 days). Patients who received nesiritide in the ED also had a fewer prolonged hospitalizations, defined as >7 days (adjusted OR: 0.516, 95% CI: 0.444 to 0.599), fewer ICU transfers (adjusted OR: 0.301, 95% CI: 0.206 to 0.440), and a significantly greater chance of being discharged to home (adjusted OR: 1.154, 95% CI: 1.005 to 1.325).

These consistent data support the hypothesis that the observed outcome differences result from the effect of time-to-treatment rather than the results of any specific therapy. They may also explain the association between delayed iBNP levels and delayed treatment. Because there is a penalty for delayed therapy as well as a penalty for erroneous therapy, a treatment delay until iBNP diagnostic confirmation may not be unreasonable, as long as iBNP data are available very soon after presentation. In the present study, the longer it took for treatment, the worse the prognosis. This is true except for the first quartile, where patients were likely much sicker and therefore recognized as HF and treated earlier.

In unadjusted analysis, within each quartile of time to diuretic, greater BNP levels were associated with a poorer prognosis. The strength of this association decreased with adjustment for variables such as blood pressure and renal function, but both BNP and time to diuretic remained independent predictors of mortality. Previous data from the ADHERE registry database have shown that initial iBNP levels are highly predictive of in-hospital mortality for both systolic dysfunction and HF with preserved function (9,17). That study used a larger database that included all hospitalized HF patients. In this study, we looked at only patients who presented to an ED, had a timed BNP draw, and had a time notation as to when the first intravenous diuretic was given.

Time-to-treatment was associated with subsequent downstream outcomes. Patients who received prompt treatment had shorter ED stays and a greater likelihood of being asymptomatic at subsequent hospital discharge. In contrast, across time-to-treatment quartiles, delayed therapy had the most notable adverse impact in those with the greatest iBNP levels.

Toward improving the "door-to-diuretic time." Because rapid assays for iBNP are widely available, we believe that routinely obtaining iBNP data as part of the initial evaluation of dyspneic patients would likely shorten time-to-treatment and may improve outcomes. Data from both the BASEL (B-type natriuretic peptide for Acute Shortness of breath EvaLuation) study (18) and the IMPROVE CHF (N-Terminal pro-B-Type Natriuretic Peptide Improves the

Management of Patients with Suspected Acute Decompensated Heart Failure) study (19) suggest that algorithms that include NP testing from the point of ED entrance to hospital discharge shorten ED and hospital stay, reduce costs, and reduce 60-day rehospitalization rates.

Study limitations. Potential limitations of the current analysis must be acknowledged. Because the ADHERE registry does not contain specific patient identifiers, the cohorts analyzed may contain multiple distinct admissions for the same patient. However, this issue should not have influenced the study results; the principle outcome parameters, timing of treatment and in-hospital mortality as it relates to the timing and level of admission iBNP, are specific to individual hospitalization episodes.

Also, because of the lack of patient identifiers, information regarding patient status after hospital discharge is not available. Differences in disease assessment, background medical therapy for HF, ED treatments, and documentation patterns at participating institutions could have influenced our findings. The time to iBNP and time to IV diuretic treatment may be proxies for the overall quality of ED care. These differences in overall ED performance may help to account for the differences in in-hospital mortality observed.

These data may not apply to patients who are cared for in settings that differ substantially from those institutions in the ADHERE registry. Each patient's actual timing of treatment and risk for in-hospital mortality may be influenced by many factors not measured or considered in this analysis. This study used results of various commercially available BNP assays rather than results from a single central core laboratory. Although this methodology may introduce great variability to iBNP testing results, this approach makes these findings more applicable to clinical practice.

Conclusions

These data from the ADHERE registry demonstrate that delayed measurement of iBNP levels is strongly associated with delay in treatment for ADHF. Delays in ED treatment for ADHF were modestly associated with increased mortality during hospitalization, independent of other prognostic variables. This effect occurred across a wide spectrum of initial iBNP levels but was most notable in patients with greater iBNP levels, suggesting that the impact of treatment delay may be amplified in more severely ill patients. Interpreting our findings in the context of previous studies, prompt measurement of iBNP levels should be considered as part of the immediate initial evaluation in patients with suspected ADHF in the ED setting.

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Key Words: B-type natriuretic peptide ■ heart failure ■ mortality ■ registries ■ diuretics.