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In-Hospital Mortality in Patients With Acute Decompensated Heart Failure Requiring Intravenous Vasoactive Medications

An Analysis From the Acute Decompensated Heart Failure National Registry (ADHERE)

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OBJECTIVES We sought to compare the in-hospital mortality of patients with acute decompensated heart failure (ADHF) who were receiving parenteral treatment with one of four intravenous vasoactive medications.

BACKGROUND There are limited data regarding the effects of the choice of intravenous vasoactive medication on in-hospital mortality in patients hospitalized with ADHF.

METHODS This was a retrospective analysis of observational patient data from the Acute Decompensated Heart Failure National Registry (ADHERE), a multicenter registry designed to prospectively collect data on each episode of hospitalization for ADHF and its clinical outcomes. Data from the first 65,180 patient episodes (October 2001 to July 2003) were included in this analysis. Cases in which patients received nitroglycerin, nesiritide, milrinone, or dobutamine were identified and reviewed (n = 15,230). Risk factor and propensity score-adjusted odds ratios (ORs) for in-hospital mortality were calculated.

RESULTS Patients who received intravenous nitroglycerin or nesiritide had lower in-hospital mortality than those treated with dobutamine or milrinone. The risk factor and propensity score-adjusted ORs for nitroglycerin were 0.69 (95% confidence interval [CI] 0.53 to 0.89, $p \leq 0.005$) and 0.46 (94% CI 0.37 to 0.57, $p \leq 0.005$) compared with milrinone and dobutamine, respectively. The corresponding values for nesiritide compared with milrinone and dobutamine were 0.59 (95% CI 0.48 to 0.73, $p \leq 0.005$) and 0.47 (95% CI 0.39 to 0.56, $p \leq 0.005$), respectively. The adjusted OR for nesiritide compared with nitroglycerin was 0.94 (95% CI 0.77 to 1.16, $p = 0.58$).

CONCLUSIONS Therapy with either a natriuretic peptide or vasodilator was associated with significantly lower in-hospital mortality than positive inotropic therapy in patients hospitalized with ADHF. The risk of in-hospital mortality was similar for nesiritide and nitroglycerin. (J Am Coll Cardiol 2005;46:57–64) © 2005 by the American College of Cardiology Foundation

Heart failure (HF) is a major and growing public health concern, significantly impairing quality of life and reducing life expectancy for nearly five million Americans (1). It is the leading cause of hospitalization in patients older than 65 years of age and is a primary hospital discharge diagnosis in approximately 1 million people of all ages each year (1,2). Estimates of the direct costs associated with HF care in the U.S. range from $25 billion annually to nearly twice this amount (1,3). The majority of costs—approximately two-thirds—are attributable to the management of episodes of acute HF decompensation (i.e., hospitalization) (3). The sequelae of acute decompensated heart failure (ADHF) include prolonged in-hospital lengths of stay, unacceptably high rates of hospital readmission, and substantial rates of inpatient and outpatient morbidity and mortality (4–6).

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Although there are published recommendations guiding the evaluation and treatment of outpatients with chronic HF (7,8), no such guidelines exist for the management of ADHF. The development of such guidelines has been delayed by the lack of an adequate evidence base. In fact, until recently, little was known about the epidemiology,

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Abbreviations and Acronyms

ADHERE = Acute Decompensated Heart Failure National Registry
ADHF = acute decompensated heart failure
BUN = blood urea nitrogen
CI = confidence interval
HF = heart failure
IV = intravenous
LVEF = left ventricular ejection fraction
OR = odds ratio

natural history, and treatment outcomes of patients with ADHF, and few randomized controlled trials have evaluated patients with HF in this setting. The Acute Decompensated Heart Failure National Registry (ADHERE) was developed to address this knowledge deficit (9).

The ADHERE is a large, multicenter registry designed to prospectively collect data on episodes of ADHF hospitalization beginning with the point of initial care in the hospital or emergency department and ending with the patient's discharge, transfer out of the hospital, or in-hospital death. Registry-participating sites include more than 275 community, tertiary, and academic medical centers from all regions of the U.S. and are representative of the nation's hospitals as a whole. The registry provides a unique opportunity to evaluate how patients admitted with HF are managed under "real-world" treatment conditions.

On the basis of previous observations (10–12), we postulated that the choice of intravenous (IV) vasoactive therapy might influence inpatient outcome in patients with ADHF. Specifically, we hypothesized that in ADHERE, IV natriuretic peptides and/or IV vasodilators would be associated with lower rates of in-hospital mortality than would IV positive inotropic agents when patients were evaluated using proper adjustment for baseline differences predicting both treatment selection (using propensity score) and the risk of in-hospital mortality (using multivariable regression analysis). This analysis was undertaken in the first 65,180 patient cases entered into the ADHERE registry through July 2003.

METHODS

The primary objectives of the ADHERE registry are to describe the demographic and clinical characteristics of patients hospitalized with ADHF, characterize the initial emergency department evaluation and subsequent inpatient management, and identify trends and changes in medical management over time (9). In addition, the registry was designed to track adherence to quality measures and to assist hospitals in evaluating and improving quality of care for patients hospitalized with ADHF. A Scientific Advisory Committee participated in the design of ADHERE (Appendix). This committee oversees the ongoing conduct of the registry and has full access to the registry data.

Patients and data collection. Consecutive patients who are admitted to a participating acute care hospital and given a discharge diagnosis of HF are eligible for entry into the registry. Patients are excluded if HF is not the principal focus of diagnosis or treatment during the admission or if their medical record cannot be accessed for administrative reasons. Otherwise, and in contrast to a clinical trial, there are no inclusion or exclusion criteria for enrollment in the ADHERE. Patient demographics, medical history, clinical presentation, laboratory results, treatment course, and clinical outcomes data are collected by chart review and entered using a Web-based electronic data capture system via an electronic case report form. Patient identifiers are not used in the collection of data. For our study, medical institution review board approval for data collection was obtained at participating centers, as required.

Mortality analysis. The present analysis was designed to compare the effects of four different IV vasoactive medications—nitroglycerin, nesiritide, milrinone, and dobutamine—on the rates of in-hospital mortality in patients with ADHF. The effects of nitroprusside could not be assessed because there were inadequate patient numbers, i.e., <1% of the total study population (92% of whom also received concomitant nesiritide, nitroglycerin, dobutamine, or milrinone), for meaningful statistical analysis. In contrast to randomized controlled trials, all therapeutic regimens captured in the ADHERE database are based on clinician judgment and not on a study protocol. Such imbalances may not only influence treatment selection, but they may predict outcome (in this case, in-hospital mortality). Thus, imbalances between groups require adjustment for baseline differences to provide valid between-group comparisons. Before and after such adjustments, the following pair-wise comparisons were conducted on ADHERE registrants: nitroglycerin versus milrinone, nitroglycerin versus dobutamine, nesiritide versus milrinone, nesiritide versus dobutamine, nesiritide versus nitroglycerin, and dobutamine versus milrinone.

The comparison of in-hospital mortality between pairs of treatments involved several steps. First, the important predictors of mortality were identified based on all patients enrolled in ADHERE using classification and regression tree analysis (CART, version 5.0, Salford Systems, San Diego, California) of 38 variables describing patients' baseline characteristics and clinical presentation (Table 1). CART is an empiric, statistical method based on recursive partitioning analyses (13). It segregates the different values of a classification variable through a binary decision tree composed of a progression of binary splits on the values of the predictor variables. Patients with missing predictor variables were included in the analysis using "surrogate" variables containing information similar to that contained in the primary splitters. The tree was constrained to have a minimum node size of 1,000 patient cases in the parent nodes and a minimum final node size of 500 patient cases. In addition, a 10-fold cross-validation was used to assess the predictive ability of the tree model. The final tree model was con-

Table 1. Variables Tested for Their Predictive Potential for In-Hospital Mortality

Demographic characteristics
Age
Height
Race
Gender
Baseline clinical characteristics
BNP concentration
BUN concentration
Congestion on first chest X-ray
Creatinine concentration
DBP
Duration of symptoms before hospitalization
Elevated cardiac enzymes (troponin I positive or ≥1 ng/ml; troponin T positive or ≥0.1 ng/ml; CK-MB >5% of total CK)
Heart rate
Hemoglobin concentration
LVEF (<40% or moderately/severely impaired ejection fraction at presentation or prehospitalization
NYHA functional classification at presentation or pre-hospitalization
Presence of dyspnea at rest
Presence of fatigue
Presence of peripheral edema
Presence of rales
QRS duration >120 ms
Sodium concentration
SBP
Weight
Coexisting conditions
History of atrial fibrillation
History of COPD/asthma
History of chronic renal insufficiency
History of CAD
History of diabetes
History of hyperlipidemia/dyslipidemia
History of hypertension
History of ischemic heart disease
History of heart failure
History of myocardial infarction
History of revascularization
History of PVD
History of stroke
History of ventricular tachycardia or fibrillation
Other
Insurance type (Medicare/Medicaid vs. other)

BNP = B-type natriuretic peptide; BUN = blood urea nitrogen; CAD = coronary artery disease; CK-MB = creatinine kinase-MB fraction; COPD = chronic obstructive pulmonary disease; DBP = diastolic blood pressure; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PVD = peripheral vascular disease; SBP = systolic blood pressure.

firmed by logistic regression with the criterion of $p < 0.001$ for inclusion in the model. Continuous predictors were dichotomized based on cutoff points suggested by the tree analysis, and the odds ratios (ORs) for death were calculated, along with corresponding 95% confidence intervals (CIs), for each predictor.

Second, to adjust for differences in baseline clinical and demographic characteristics between patient treatment groups, a propensity score analysis was conducted for each pair-wise comparison using CART models (14–16). The propensity score is the conditional probability of assignment to a particular treatment given observed covariates; this score has been shown to produce unbiased estimates of the treatment effect in observational studies. Patients taking both medications were excluded from each pair-wise comparison. The trees were constrained to have a minimum node size of 900 patient cases in the parent nodes and a minimum final node size of 300 patient cases.

The final step in the analysis was logistic regression to compare the mortality of patients treated with different medications, adjusting for mortality risk factors, treatment propensity score, and gender. The use of mortality risk factors as dichotomous variables with cutoff points identified by tree analysis led to equivalent results; therefore, mortality risk factors (except for dyspnea) and propensity score were included as continuous variables in the final logistic regression model to fully use the information available in these variables. The Hosmer-Lemeshow test was used to assess goodness of fit. The area under the receiver operator curve was used to assess model discrimination. Unadjusted ORs, ORs adjusted for risk factors, and ORs adjusted for risk factors and propensity score, along with their corresponding 95% CIs and p values, were reported. Because of multiple pair-wise comparisons, only p values <0.008 were considered significant using strict Bonferroni correction. All analyses were performed using SAS version 8.0 (SAS Institute, Cary, North Carolina), unless noted otherwise.

RESULTS

Patient demographics and drug administration. Between October 2001 and July 2003, a total of 65,180 patient cases from 263 hospitals were enrolled in the ADHERE. On average, patients were 72.5 ± 13.9 years of age. Fifty-two percent were women. Fifty-eight percent had coronary artery disease; a history of hypertension (72%), diabetes mellitus (44%), atrial fibrillation (30%), and renal insufficiency (29%) were common types of comorbidity. During hospitalization, 15,230 (23.4%) of these cases received IV vasoactive treatment consisting of nitroglycerin (n = 6,549), nesiritide (n = 5,220), milrinone (n = 2,021), or dobutamine (n = 4,226). The mean maximal dose during the initial 24 h of the infusion was 24.9 μg/min for nitroglycerin, 0.02 μg/kg/min for nesiritide, 0.54 μg/kg/min for milrinone, and 6.05 μg/kg/min for dobutamine. Sixteen percent of patient cases received more than one of these medications, with 14.2% of patient cases receiving two study medications, 1.9% receiving three study medications, and 0.1% receiving all four study medications. Demographic and clinical characteristics of registry patients by treatment are listed in Table 2.

In general, patients treated with IV vasoactive agents were more likely than other registry participants to be younger and male and to have ischemic HF, coronary artery disease, renal insufficiency, serum creatinine concentrations of ≥2 mg/dl, and lower left ventricular ejection fractions (LVEFs). Patients treated with dobutamine or milrinone tended to have higher blood urea nitrogen (BUN) levels,

Table 2. Demographic Characteristics, Baseline Clinical Characteristics, and Outcome Measures for ADHERE Patients

Parameter	Nitroglycerin* (n = 6,549)	Nesiritide* (n = 5,220)	Milrinone* (n = 2,021)	Dobutamine* (n = 4,226)	All Other Patients† (n = 49,950)
Demographics					
Age (yrs)					
Mean ± SD	71.2 ± 13.4	70.9 ± 13.6	67.3 ± 14.0	70.4 ± 13.5	73.1 ± 14.0
Median (Q1, Q3)‡	73.4 (62.7, 81.1)	73.3 (62.8, 81.0)	69.7 (58.4, 77.6)	73.0 (62.8, 80.2)	75.8 (64.5, 83.3)
Gender					
Female, n (%)	3,467 (53)	2,215 (42)	668 (33)	1,559 (37)	26,948 (54)
Medical history					
Ischemic heart failure etiology, n/total (%)	1,203/2,259 (53)	1,588/2,769 (57)	778/1,253 (62)	1,440/2,416 (60)	8,125/17,615 (46)
CAD, n/total (%)	4,163/6,548 (64)	3,599/5,220 (69)	1,345/2,021 (67)	2,952/4,226 (70)	27,613/49,948 (55)
Renal insufficiency, n/total (%)	2,061/6,549 (31)	2,025/5,220 (39)	807/2,021 (40)	1,759/4,226 (42)	13,579/49,949 (27)
Atrial fibrillation, n/total (%)	1,491/6,549 (23)	1,782/5,220 (34)	662/2,021 (33)	1,434/4,226 (34)	15,327/49,949 (31)
Diabetes, n/total (%)	3,175/6,549 (48)	2,592/5,220 (50)	879/2,021 (43)	1,909/4,226 (45)	21,561/49,950 (43)
Hypertension, n/total (%)	5,247/6,549 (80)	3,695/5,220 (71)	1,182/2,021 (58)	2,633/4,226 (62)	36,010/49,950 (72)
Hyperlipidemia, n/total (%)	2,644/6,549 (40)	2,043/5,220 (39)	758/2,021 (38)	1,609/4,226 (38)	16,350/49,949 (33)
PVD, n (%)	1,266/6,549 (19)	1,088/5,220 (21)	366/2,021 (18)	811/4,226 (19)	8,406/49,950 (17)
COPD/asthma, n (%)	1,962/6,549 (30)	1,615/5,220 (31)	537/2,021 (27)	1,286/4,226 (30)	15,520/49,949 (31)
Baseline oral neurohormonal medications					
Beta-blocker, n/total (%)	3,369/6,543 (52)	2,804/5,219 (54)	1,125/2,020 (56)	2,001/4,224 (47)	22,277/49,912 (45)
ACE inhibitor, n/total (%)	2,757/6,543 (42)	2,282/5,219 (44)	933/2,020 (46)	1,856/4,224 (44)	20,160/49,912 (40)
ARB, n/total (%)	773/6,543 (12)	644/5,219 (12)	260/2,020 (13)	524/4,224 (12)	5,591/49,912 (11)
Spironolactone, n/total (%)	480/6,543 (7)	870/5,219 (17)	492/2,020 (24)	800/4,224 (19)	4,280/49,912 (9)
Initial evaluation					
BUN (mg/dl)					
Mean ± SD	30.3 ± 19.2	37.5 ± 23.6	41.9 ± 26.5	42.5 ± 27.1	30.6 ± 20.2
Median (Q1, Q3)	24.0 (17.0, 38.0)	31.0 (20.0, 49.0)	35.0 (23.0, 55.0)	35.0 (22.4, 56.0)	25.0 (17.0, 38.0)
Creatinine (mg/dl)					
Mean ± SD	1.9 ± 1.9	1.7 ± 1.0	1.8 ± 1.1	1.9 ± 1.2	1.7 ± 1.7
Median (Q1, Q3)	1.3 (1.0, 1.9)	1.5 (1.1, 2.1)	1.6 (1.2, 2.1)	1.6 (1.2, 2.3)	1.3 (1.0, 1.8)
Creatinine ≥2 mg/dl, n/total (%)	1,450/6,454 (22)	1,319/5,119 (26)	541/1,939 (28)	1,341/4,124 (33)	9,035/49,084 (18)
Sodium (mmol/l)					
Mean ± SD	138.7 ± 4.4	137.6 ± 4.9	136.5 ± 5.3	136.5 ± 5.3	138.3 ± 4.9
Median (Q1, Q3)	139.0 (136.0, 142.0)	138.0 (135.0, 141.0)	137.0 (134.0, 140.0)	137.0 (134.0, 140.0)	139.0 (136.0, 141.0)
Hemoglobin (g/dl)					
Mean ± SD	12.7 ± 2.7	12.3 ± 2.4	12.6 ± 2.5	12.6 ± 2.8	12.4 ± 2.7
Median (Q1, Q3)	12.5 (11.0, 14.0)	12.1 (10.7, 13.7)	12.2 (10.9, 13.8)	12.3 (10.8, 13.9)	12.2 (10.8, 13.7)
SBP (mm Hg)					
Mean ± SD	163.0 ± 37.1	137.4 ± 32.2	121.3 ± 27.4	124.0 ± 29.3	144.6 ± 31.0
Median (Q1, Q3)	160.0 (135.5, 191.0)	133.0 (113.0, 156.0)	117.0 (101.0, 138.0)	120.0 (102.0, 141.0)	142.0 (122.0, 164.0)
SBP <90 mm Hg, n/total (%)	60/6,420 (1)	155/5,192 (3)	160/2,002 (8)	347/4,196 (8)	886/49,636 (2)
DBP (mm Hg)					
Mean ± SD	88.8 ± 25.3	76.4 ± 19.8	70.1 ± 17.6	70.1 ± 18.2	77.4 ± 19.1
Median (Q1, Q3)	86.0 (70.0, 105.0)	74.0 (62.0, 88.0)	69.0 (59.0, 80.0)	69.0 (58.0, 80.0)	76.0 (64.0, 89.0)
Heart rate (beats/min)					
Mean ± SD	95.9 ± 24.0	88.3 ± 21.7	87.3 ± 21.0	87.3 ± 21.2	88.0 ± 21.6
Median (Q1, Q3)	94.0 (78.0, 112.0)	85.0 (72.0, 102.0)	84.0 (72.0, 100.0)	84.0 (72.0, 100.0)	85.0 (72.0, 100.0)
QRS >120 ms, n/total (%)	1,804/5,980 (30)	2,013/4,533 (44)	834/1,607 (52)	1,753/3,573 (49)	13,470/43,305 (31)
LVEF <40% or moderate-to-severe impairment, n/total (%)	3,000/5,565 (54)	3,219/4,539 (71)	1,639/1,847 (89)	3,099/3,715 (83)	19,221/38,961 (49)
Dyspnea at rest, n/total (%)	3,115/6,549 (48)	2,150/5,220 (41)	665/2,021 (33)	1,701/4,226 (40)	16,554/49,950 (33)
Peripheral edema, n/total (%)	3,979/6,549 (61)	3,846/5,220 (74)	1,328/2,021 (66)	2,898/4,226 (69)	33,164/49,950 (66)
Fatigue, n/total (%)	1,735/6,549 (26)	1,954/5,220 (37)	902/2,021 (45)	1,818/4,226 (43)	16,280/49,950 (33)
Rales, n/total (%)	5,028/6,549 (77)	3,653/5,220 (70)	1,269/2,021 (63)	2,862/4,226 (68)	33,546/49,950 (67)
Time to therapy (h)					
Mean ± SD	15.9 ± 52.8	30.2 ± 64.0	54.3 ± 106.0	48.6 ± 82.0	NA
Median (Q1, Q3)	1.3 (0.5, 5.1)	7.8 (3.3, 28.1)	18.4 (4.6, 67.7)	17.6 (4.0, 62.5)	NA
Outcome measures					
ICU length of stay (d)					
Mean ± SD	3.9 ± 5.2	4.6 ± 5.8	6.9 ± 8.3	6.1 ± 7.4	3.2 ± 4.0
Median (Q1, Q3)	2.4 (1.4, 4.3)	3.2 (2.0, 5.4)	4.3 (2.4, 8.0)	4.0 (2.1, 7.1)	2.0 (1.0, 3.9)
Total length of stay (d)					
Mean ± SD	7.1 ± 7.1	7.9 ± 7.1	10.9 ± 10.0	10.0 ± 9.0	5.3 ± 4.5
Median (Q1, Q3)	5.1 (3.2, 8.4)	6.0 (3.8, 9.9)	8.0 (4.7, 13.9)	7.7 (4.7, 12.6)	4.1 (2.7, 6.6)
Mortality, n/total (%)	310/6,549 (4.7)	370/5,220 (7.1)	248/2,021 (12.3)	589/4,226 (13.9)	1,563/49,950 (3.1)

*Patients receiving more than one therapy are counted in multiple treatment groups. †Patients not receiving nesiritide, nitroglycerin, dobutamine, or milrinone. ‡25th percentile (Q1) and 75th percentile (Q3).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ICU = intensive care unit; other abbreviations as in Table 1.

Table 3. Mortality Predictors Selected by Classification Tree Model

Parameter	Died (n = 2675)	Survived (n = 62,505)	OR of Death (95% CI)
Age (yrs)			
Mean ± SD	77.4 ± 12.2	72.3 ± 14.0	
Median (Q1, Q3)*	79.6 (71.3, 86.0)	74.9 (63.7, 82.5)	
Age >78 vs. ≤78			1.88 (1.74–2.04)
BUN (mg/dl)			
Mean ± SD	47.9 ± 29.7	31.2 ± 20.5	
Median (Q1, Q3)	40.0 (26.0, 61.0)	25.0 (17.0, 39.0)	
BUN >42 vs. ≤42			3.34 (3.08–3.62)
Serum Cr (mg/dl)			
Mean ± SD	2.1 ± 1.7	1.7 ± 1.7	
Median (Q1, Q3)	1.7 (1.2, 2.5)	1.3 (1.0, 1.8)	
Cr >3.2 vs. ≤3.2			1.99 (1.78–2.24)
SBP (mm Hg)			
Mean ± SD	124.9 ± 29.9	145.0 ± 32.4	
Median (Q1, Q3)	122 (104, 143)	142 (121, 165)	
SBP ≤115 vs. >115			3.09 (2.85–3.35)
DBP (mm Hg)			
Mean ± SD	67.7 ± 18.5	78.3 ± 20.1	
Median (Q1, Q3)	67 (55, 78)	76 (64, 90)	
DBP ≤55 vs. >55			2.87 (2.62–3.14)
Serum sodium (mmol/l)			
Mean ± SD	136.5 ± 6.2	138.2 ± 4.8	
Median (Q1, Q3)	137 (133, 140)	139 (136, 141)	
Sodium ≤134 vs. >134			2.26 (2.08–2.47)
HR (beats/min)			
Mean ± SD	90.7 ± 23.3	88.5 ± 21.8	
Median (Q1, Q3)	88 (74, 105)	86 (73, 101)	
HR >84 vs. ≤84			1.20 (1.11–1.30)
Dyspnea at rest, n (%)	1,220 (46%)	21,757 (35%)	1.57 (1.45–1.70)

*25th percentile (Q1) and 75th percentile (Q3).
CI = confidence interval; Cr = creatinine; HR = heart rate; OR = odds ratio; other abbreviations as in Table 1.

lower blood pressure, greater QRS duration, and lower LVEF than patients who were treated with nesiritide or nitroglycerin. Relative to nitroglycerin, patients treated with nesiritide tended to have higher BUN levels, serum creatinine concentrations of ≥ 2 mg/dl, lower systolic blood pressure and diastolic blood pressure, greater QRS duration, and lower LVEF. Nearly one-half (46%) of all nitroglycerin-treated patients had preserved left ventricular systolic function (LVEF ≥40%). Females represented a smaller percentage of patients treated with inotropes than patients treated with vasodilators. Nitroglycerin therapy was provided earlier than nesiritide, which in turn was administered earlier than either inotrope.

In-hospital outcome. The mean length of hospital stay and mean length of stay in the intensive care unit/coronary care unit for patients receiving IV vasoactive agents were longer than those for other registry patients (Table 2). Patients treated with nitroglycerin or nesiritide had shorter overall lengths of stay in the hospital and in the intensive care unit/coronary care units than patients treated with milrinone or dobutamine. Furthermore, unadjusted in-hospital mortality was lower among patients treated with a vasodilator or natriuretic peptide compared with patients treated with an inotrope (4.7% and 7.1% for patients receiving nitroglycerin and nesiritide, respectively, compared with 12.3% and 13.9% for patients receiving milrinone and dobutamine, respectively). Because there were substantial differences in baseline characteristics and risk factors between these treatment groups, adjustments for propensity of receiving a particular IV vasoactive treatment were performed to compare mortality rates.

Of the 65,180 patients analyzed in the ADHERE registry, 2,675 (4.1%) died while hospitalized. Table 3 shows the eight parameters that were predictive of in-hospital mortality based on the CART model. Risk of in-hospital mortality was significantly increased in patients with BUN levels >42 mg/dl (OR = 3.34), systolic blood pressure ≤115 mm Hg (OR = 3.09), diastolic blood pressure ≤55 mm Hg (OR = 2.87), serum sodium ≤134 mmol/l (OR = 2.26), creatinine levels >3.2 mg/dl (OR = 1.99), age >78 years (OR = 1.88), dyspnea at rest (OR = 1.57), and heart rate >84 beats/min (OR = 1.20).

The unadjusted ORs for in-hospital mortality, ORs adjusted for the eight covariates and gender, and ORs adjusted for the covariates and propensity score and their corresponding CIs and p values are shown in Table 4. Overall, survival was better in patients receiving nitroglycerin or nesiritide than in patients receiving milrinone or dobutamine for both unadjusted and adjusted ORs. The unadjusted odds of mortality were higher with nesiritide than with nitroglycerin, but once proper adjustments were made for covariates and propensity score, the two drugs had

Table 4. Mortality Odds Ratios in Pair-Wise Treatment Comparisons

Analysis*	NTG (n = 6,055) vs. MIL (n = 1,660)	NTG (n = 5,713) vs. DOB (n = 3,478)	NES (n = 4,663) vs. MIL (n = 1,534)	NES (n = 4,270) vs. DOB (n = 3,301)	NES (n = 4,402) vs. NTG (n = 5,668)	DOB (n = 3,656) vs. MIL (n = 1,496)
Unadjusted	0.34 (0.28–0.41)†	0.24 (0.20–0.28)†	0.53 (0.44–0.64)†	0.37 (0.32–0.44)†	1.64 (1.38–1.94)†	1.39 (1.15–1.68)†
Adjusted for covariates‖	0.69 (0.54–0.88)†	0.46 (0.38–0.57)†	0.59 (0.48–0.73)†	0.47 (0.39–0.56)†	0.95 (0.78–1.16)‡	1.27 (1.04–1.56)§
Adjusted for covariates and propensity score¶	0.69 (0.53–0.89)†	0.46 (0.37–0.57)†	0.59 (0.48–0.73)†	0.47 (0.39–0.56)†	0.94 (0.77–1.16)‡	1.24 (1.03–1.55)§

Hosmer-Lemeshow goodness-of-fit test not significant at 5% levels for the models adjusted for risk factors and/or propensity, except for covariate-adjusted NTG vs. DOB comparison, where p = 0.04. Area under the receiver operator curve = 0.70 or higher. Because of multiple pair-wise comparisons, only p values <0.008 were considered significant using Bonferroni correction. *Patients taking both medications were excluded from each pair-wise analysis. †p < 0.005. ‡p = 0.58. §p = 0.021 for covariate adjustment and 0.027 for covariate and propensity score adjustment. ‖Covariates include age, gender, SBP, DBP, BUN, creatinine, sodium, heart rate, and dyspnea. ¶Covariates included in the propensity score by treatment comparison are: NES vs. DOB: SBP, sodium, BUN, creatinine, age, weight, LVEF, edema; NES vs. MIL: SBP, age, LVEF, dyspnea, weight; NTG vs. DOB: SBP, sodium, BUN, heart rate, LVEF, symptom duration; NTG vs. MIL: SBP, BUN, LVEF, symptom duration, dyspnea, QRS >120 ms, previous revascularization; NES vs. NTG: SBP, BUN, creatinine, LVEF, symptom duration, edema, previous HF, QRS >120 ms; DOB vs. MIL: SBP, age, hemoglobin, heart rate, dyspnea, VTF.

DOB = dobutamine; HF = heart failure; LVEF = left ventricular ejection fraction; MIL = milrinone; NES = nesiritide; NTG = nitroglycerin; OR = odds ratio; VTF = ventricular tachycardia/fibrillation; other abbreviations as in Table 1.

similar effects on mortality. Patients receiving nesiritide had a covariate- and propensity score-adjusted OR for mortality of 0.94 (95% CI 0.77 to 1.16, p = 0.58) compared with patients receiving nitroglycerin. The unadjusted OR was higher for dobutamine than for milrinone and remained higher once adjusted for covariates and propensity score. Patients receiving dobutamine had a covariate- and propensity score-adjusted OR of 1.24 (95% CI 1.03 to 1.55, p = 0.027) compared with patients receiving milrinone. Of the patients who received vasoactive agents, 579 (3.8%) had a systolic blood pressure <90 mm Hg. Exclusion of these patients from the analyses did not significantly alter the adjusted mortality ORs between treatment groups.

DISCUSSION

The present study demonstrates significant differences in outcome, particularly for in-hospital mortality, based on the choice of IV vasoactive medication used in the treatment of ADHF. Specifically, the present analysis contributes to our fund of knowledge by showing that mortality is similar with the natriuretic peptide nesiritide and the vasodilator nitroglycerin but significantly higher with the use of the positive inotropic agents dobutamine and milrinone. This observation may have significant implications for IV drug selection in the management of such patients, suggesting that natriuretic peptides and vasodilators should be preferred over positive inotropic agents in patients with ADHF requiring treatment with an IV vasoactive drug. Each of these IV vasoactive agents is commonly used to treat ADHF patients, and each has a unique mechanism of action and risk/benefit profile (17–19).

Dobutamine is a direct-acting positive inotropic agent with primary activity resulting from the stimulation of beta-adrenergic receptors in the heart (17). Milrinone, a cyclic adenosine monophosphate-specific phosphodiesterase inhibitor, produces positive inotropic and vasodilatory effects independent of beta-adrenergic receptor stimulation but acts in the heart via the same signal-transduction pathway as dobutamine (18,19). Nitroglycerin reduces preload and afterload by dilating peripheral capacitance and resistance vessels through a direct interaction with receptors on vascular smooth muscle cells. Nesiritide is the first drug of its class, the natriuretic peptides, to be used clinically in the management of ADHF. It provides benefit in patients with ADHF via a combination of neurohormonal as well as hemodynamic and renal effects (20–24).

Given these various mechanisms of action, it is not surprising that dobutamine is associated with an increase in myocardial oxygen consumption, heart rate, and risk of arrhythmias (25,26), whereas milrinone produces tachycardia and other arrhythmias and is limited by hypotension in many patients (10,26). Thus, the clinical "cost" of positive inotropic therapy may manifest as life-threatening adverse events in patients with ADHF. In addition, stimulation of the beta-adrenergic signal-transduction pathway has been implicated in HF disease progression, providing the rationale for beta-adrenergic receptor blockade in the treatment of chronic HF (27). The present analysis from the ADHERE suggests that such stimulation, when delivered exogenously, also may exert a deleterious effect on the natural history of ADHF. These findings are supported by other observations, including those from randomized controlled trials demonstrating worse outcomes with positive inotropic agents compared with placebo (i.e., standard care) (10,28,29). Vasodilators and natriuretic peptides lower ventricular filling pressures and systemic vascular resistance and improve cardiac performance indirectly via these unloading effects (24,30). They do not stimulate tachycardia or other arrhythmias but do exhibit the risk of hypotension (25,31). However, in controlled studies, the risk of symptomatic hypotension is low (4% to 5%) with either nesiritide or the nitrovasodilators (11). Despite this risk of hypotension, the differentiated safety concerns in the present analysis from the ADHERE favors the use of nesiritide or vasodilators over positive inotropic agents in the treatment of ADHF.

Because nitroglycerin and nesiritide appear to be equally safe in the treatment of ADHF, other effects must be considered when choosing between these agents. At the present time, nitroglycerin has been studied more extensively and used in patients with acute ischemic syndromes. Thus, chest pain or an acute coronary syndrome precipitat-

ing or accompanying ADHF may represent a scenario in which nitroglycerin would be preferred. However, natriuretic peptides also demonstrate coronary vasodilating effects, and one study of nesiritide included a small number of patients with HF in the setting of an acute coronary syndrome (11). Future studies may better define the role of nesiritide in such patients. Moreover, in patients with HF, nitroglycerin is associated with activation of the renin-angiotensin system and fluid retention (32), whereas nesiritide suppresses vasoconstrictive and anti-natriuretic hormones (23,24). Nesiritide also exhibits favorable renal effects in patients with ADHF (21,33). Thus, patients with fluid retention and/or renal insufficiency may be better candidates for treatment with nesiritide.

In a randomized controlled trial of acute decompensation of chronic heart failure, nesiritide provided significant hemodynamic and clinical benefits. The Vasodilation in the Management of Acute Congestive Heart Failure (VMAC) trial was a randomized, double-blind, placebo-controlled comparison of nesiritide and nitroglycerin (in addition to standard therapy) in patients with ADHF (11). Reductions in pulmonary capillary wedge pressure were significantly greater with nesiritide than with nitroglycerin, starting with the first measurement at 15 min and persisting throughout the first day, with no evidence of attenuation of effect (11,30). In addition, when compared with placebo, nesiritide, but not nitroglycerin, significantly lowered systemic vascular resistance and increased cardiac index at 1 h and significantly reduced dyspnea within 3 h after initiation of therapy (11). Finally, nesiritide produced a trend toward improvement in global clinical status at 24 h relative to nitroglycerin (11).

The present analysis of the ADHERE database is limited by a number of factors. First, the data are observational and the analysis is retrospective. Second, clinician judgment rather than a study protocol guided the selection of IV vasoactive medication used in a particular patient. However, to control for such judgment, propensity scores were developed to eliminate the effects of selection bias inherent in nonrandomized trials (34). A propensity score is a scalar summary of an individual's covariate information that is equal to that individual's conditional probability of treatment, given these covariates (14,34,35). Consequently, propensity scores are balancing scores that reduce treatment bias (14). The observed differences in this study between unadjusted and adjusted mortality ORs (particularly in terms of nesiritide vs. nitroglycerin) underscore the need to perform covariate and risk adjustments. In nonrandomized trials, balancing cohorts on the basis of propensity scores yields the same statistical effect, with respect to the included covariates, as randomization does in controlled clinical trials. Recent cardiovascular trials have used propensity score analyses to permit a more rigorous adjustment for selection bias and confounding than is possible with standard analyses (36,37). In addition, a strength of this registry is that it eliminates the selection bias inherent in randomized controlled trials. For example, randomized controlled trials of HF generally enroll men, age 60 to 65 years, with left ventricular systolic dysfunction and low rates of comorbidity. In the ADHERE registry, the average age is approximately 73 years, and 52% of registrants are women. Preserved systolic function is common, and comorbidities also are much more prevalent. Thus, ADHERE provides insights into the effect of ADHF therapies in a more representative ADHF population than that which is generally enrolled in randomized clinical trials.

A third limitation is that differences in clinical characteristics between subjects who did and did not receive IV vasoactive therapy prohibited inclusion of a non-IV vasoactive control group. Furthermore, because the ADHERE registry collects data only during the period of hospitalization, the long-term effects of the various IV vasoactive therapies cannot be determined. However, with respect to these last limitations, a recent analysis of data from the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial found that patients with ADHF treated with IV vasodilators had a six-month mortality risk that is similar to that of patients with ADHF who do not require IV vasoactive medication. In contrast, patients with ADHF treated with an IV inotropic agent had a 1.8-fold increase in their six-month mortality risk (38).

In the current analysis, baseline data on cardiac and renal function, including blood pressure, LVEF, QRS duration, and BUN and serum creatinine levels, demonstrated that patients treated with nesiritide, dobutamine, and milrinone tended to be sicker and thus be at greater risk of dying, than those treated with nitroglycerin. Thus, it is not surprising that the unadjusted OR for mortality is higher with these agents than with nitroglycerin in this study. Two different well-established statistical techniques, CART analysis and propensity scores, were used to adjust for these baseline differences. Application of these techniques eliminated the apparent mortality difference between nesiritide and nitroglycerin but not the significant mortality differences between nesiritide or nitroglycerin and dobutamine or milrinone. Nonetheless, these statistical techniques are not perfect and may have failed to completely control for baseline differences between treatment groups, a limitation of this as well as all other uncontrolled retrospective analyses.

In summary, the ADHERE registry is the largest database available to characterize patients hospitalized with ADHF. Data collected from real-world analyses such as this one provide valuable information on treatment safety and efficacy that is not available from highly controlled, short-term, clinical trials of carefully selected patient populations. In the current analysis of data culled from the ADHERE, rates of in-hospital mortality in patients treated with nesiritide were similar to those in patients treated with nitroglycerin, and nesiritide or nitroglycerin were associated with a significant survival benefit compared with either dobutamine or milrinone. These mortality data support the

use of nitroglycerin or nesiritide rather than positive inotropic agents in the management of patients with ADHF who require IV vasoactive therapy. Positive inotropic agents should be considered only in patients who are refractory to treatment with vasodilators or nesiritide or in patients in impending cardiogenic shock.

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APPENDIX

For a list of the ADHERE Scientific Advisory Committee and the ADHERE Study Group, please see the July 5, 2005, issue of *JACC* at www.onlinejacc.org.