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Time-to-Furosemide Treatment and Mortality in Patients Hospitalized With Acute Heart Failure

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ABSTRACT

BACKGROUND Acute heart failure (AHF) is a life-threatening disease requiring urgent treatment, including a recommendation for immediate initiation of loop diuretics.

OBJECTIVES The authors prospectively evaluated the association between time-to-diuretic treatment and clinical outcome.

METHODS REALITY-AHF (Registry Focused on Very Early Presentation and Treatment in Emergency Department of Acute Heart Failure) was a prospective, multicenter, observational cohort study that primarily aimed to assess the association between time to loop diuretic treatment and clinical outcome in patients with AHF admitted through the emergency department (ED). Door-to-furosemide (D2F) time was defined as the time from patient arrival at the ED to the first intravenous furosemide injection. Patients with a D2F time <60 min were pre-defined as the early treatment group. Primary outcome was all-cause in-hospital mortality.

RESULTS Among 1,291 AHF patients treated with intravenous furosemide within 24 h of ED arrival, the median D2F time was 90 min (IQR: 36 to 186 min), and 481 patients (37.3%) were categorized as the early treatment group. These patients were more likely to arrive by ambulance and had more signs of congestion compared with the nonearly treatment group. In-hospital mortality was significantly lower in the early treatment group (2.3% vs. 6.0% in the nonearly treatment group; p = 0.002). In multivariate analysis, earlier treatment remained significantly associated with lower in-hospital mortality (odds ratio: 0.39; 95% confidence interval: 0.20 to 0.76; p = 0.006).

CONCLUSIONS In this prospective multicenter, observational cohort study of patients presenting at the ED for AHF, early treatment with intravenous loop diuretics was associated with lower in-hospital mortality. (Registry focused on very early presentation and treatment in emergency department of acute heart failure syndrome; UMIN000014105) (J Am Coll Cardiol 2017;69:3042–51) © 2017 by the American College of Cardiology Foundation.

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Acute heart failure (AHF) is a life-threatening disease that remains an important public health issue, with high morbidity, mortality, and economic burden. Although a paradigm shift has occurred regarding treatment of chronic systolic heart failure (HF), the management of AHF has not changed for several decades, and most clinical studies investigating several drugs targeting this population have failed to demonstrate a favorable prognostic impact (1).

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The emergency department (ED) is a major stage for hospitalized patients with AHF. In the United States, almost 1 million ED visits for AHF occur per year, with ≥80% of patients admitted (2,3). The importance of the ED phase in managing AHF has become increasingly apparent as recent post hoc studies have highlighted that although patient characteristics are important, the efficacy of any intervention/treatment may be time dependent (4–6). Therefore, recent HF guidelines and recommendations emphasized the importance of immediate diagnosis and treatment of patients presenting with AHF (7,8). However, this concept has only been evaluated using retrospective data. The REALITY-AHF (Registry Focused on Very Early Presentation and Treatment in Emergency Department of Acute Heart Failure) was a prospective multicenter study to evaluate the association between time to treatment and clinical outcome in patients with AHF presenting at the ED.

METHODS

The main objective of REALITY-AHF was to determine the prognostic impact of time to treatments for AHF performed in the acute phase. All consecutive patients with AHF hospitalized through the ED at participating hospitals were enrolled upon the initial hospital admission. Only the first hospitalization during the study period was registered. Patients were included if they were age ≥20 years and diagnosed with AHF in the ED within 3 h of their first evaluation by caregivers. The AHF diagnosis was made based on Framingham criteria (9). Exclusion criteria were: 1) treatment with an intravenous (IV) drug before ED arrival; 2) previous heart transplantation; 3) on either chronic peritoneal dialysis or hemodialysis; 4) acute myocarditis; and 5) acute coronary syndrome requiring emergent or urgent revascularization. Patients with missing B-type natriuretic peptide (BNP) or N-terminal-proBNP (NT-proBNP) data, and patients with a BNP level <100 pg/ml or NT-proBNP level <300 pg/ml at baseline were also excluded. Enrollment was performed from August 2014 to December 2015. Among the 20 participating hospitals, 9 were university hospitals and 11 were nonuniversity teaching hospitals.

Because all patients were enrolled at the ED, the time of ED arrival was recorded, and data were collected for up to 48 h from the time of ED arrival. Drug and doses of all IV treatments were recorded. Additionally, the time from arrival to the "first IV furosemide" administration was recorded for all patients because it was the primary pre-specified variable of interest. Oral medication taken within 48 h was also recorded for all HF medications, including the amount of diuretics. Baseline physical findings and blood samples were taken and evaluated in the ED for all patients. Echocardiography was performed at the ED and subsequent steady-state phases. Left ventricular ejection fraction was assessed by echocardiography at the ED and categorized into 3 groups: <35%; 35% to 50%; and >50%.

Importantly, the nature of this study did not require participants to use any particular drug or treatment strategy. The mission of the registry was to capture patients with AHF immediately after arrival to the ED and for the study enrollment process to avoid any delay or difference in the time course. Because obtaining written informed consent at the ED

ABBREVIATIONS AND ACRONYMS

AHF = acute heart failure
BNP = B-type natriuretic peptide
CI = confidence interval
D2F = door-to-furosemide
ED = emergency department
GEE = generalized estimating equation
GWTG-HF = Get With the Guidelines-Heart Failure
HF = heart failure
IQR = interquartile range
IV = intravenous
NT-proBNP = N-terminal-proBNP
OR = odds ratio

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may cause a delay in the ED management timeline, and subsequently biasing the results, we used an opt-out method for participant recruitment. All participants were notified regarding their participation in the study and it was explained that they were free to opt out of participation at any time. Our study complied with the Declaration of Helsinki and Japanese Ethical Guideline for Medical and Health Research involving Human Subjects. The study protocol was approved by the ethics committee of each participating hospital. Study information including objectives, inclusion and exclusion criteria, and the names of participating hospitals were published in the publically available University Hospital Information Network (UMIN000014105) before the first patient was enrolled.

DOOR-TO-FUROSEMIDE TIME. Patients who were treated with IV furosemide within 48 h of ED arrival were included in the present study. The exact time of the first IV furosemide administration was recorded; the time from ED arrival to the administration of the first IV furosemide was defined as the door-to-furosemide (D2F) time. Patients with missing D2F times were excluded. To distinguish IV diuretics used for treating the initial AHF symptoms from treatment for deteriorated HF symptoms caused after the initial phase, we included only patients with a D2F time <24 h. In accordance with published recommendations of the European Society of Cardiology regarding early and prehospital management of AHF, we defined early and nonearly treatment groups using the D2F time with a cutoff of 60 min (8). The primary endpoint was all-cause in-hospital mortality.

STATISTICAL ANALYSIS. Data are expressed as mean ± SD for normally distributed variables and as median with interquartile range (IQR) for non-normally distributed data. Categorical data are expressed as numbers (%). When necessary, variables were transformed for further analyses. Group differences were evaluated using Student *t* tests or Mann-Whitney *U* tests for continuous variables and chi-square or Fisher exact tests for categorical variables. The Get With the Guidelines-Heart Failure (GWTG-HF) risk score was calculated for each patient as previously described (10). The GWTG-HF risk score is based on race, age, systolic blood pressure, heart rate, blood urea nitrogen, sodium levels, and the presence of chronic obstructive pulmonary disease. The discrimination and calibration of this risk score have been well validated in Japanese patients with AHF (11); therefore, the GWTG-HF score was used as an adjustment variable in a multivariable prognostic model. Additionally, the patients were stratified according to GWTG-HF risk score quartiles and quartile groups were evaluated for differences in in-hospital mortality to examine the relationship between GWTG-HF scores at baseline and the prognostic impact of early treatment.

Univariate and multivariable logistic regression analyses were performed to evaluate the association between early treatment and in-hospital prognosis. Furthermore, generalized estimating equation (GEE) models were used to account for intrainstitutional correlations among patients. The presence of a nonlinear association between D2F time and in-hospital mortality was evaluated using a linear regression model with restricted cubic splines of 3, 4, and 5 knots. The goodness-of-fit was compared between models using an analysis of variance test.

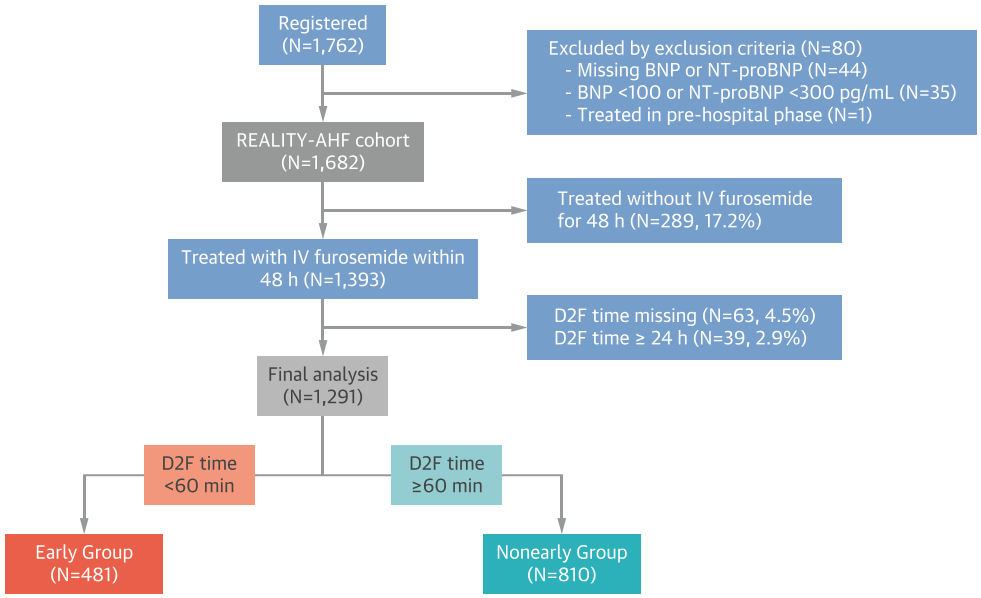
To control confounding as much as possible, propensity score matching was also performed as a sensitivity analysis. The propensity score was estimated based on a logistic model constructed with the following variables: age; sex; arrival by ambulance; baseline systolic blood pressure, diastolic blood pressure, heart rate, white blood cell count, hemoglobin, aspartate aminotransferase, alanine aminotransferase, serum sodium, blood urea nitrogen, BNP, and glucose; history of chronic obstructive pulmonary disease; presence/absence of jugular venous distension, orthopnea, peripheral edema, or rales at baseline; and prescription of an angiotensin-converting enzyme inhibitor or loop diuretics at admission. Propensity score matching was performed for the early and nonearly treatment groups with one-to-one caliper matching using a caliper width equal to 20% of the SD of the logit of the calculated propensity score (12). To assess the performance of the matching, standardized mean differences were calculated for all baseline variables and a difference below 0.1 was considered negligible (i.e., the 2 groups were well balanced) (13).

A 2-tailed p value <0.05 was considered statistically significant. Statistical analyses were performed using R, version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

During the study period, 1,762 patients meeting inclusion criteria were registered in the REALITY-AHF study (**Figure 1**). Eighty patients met exclusion criteria, leaving 1,682 patients; among these patients, 1,393 (82.8%) were given IV furosemide within 48 h of ED arrival. After excluding patients without an available D2F time or a D2F time >24 h, the final cohort for analysis included 1,291 patients.

FIGURE 1 Study Flow



A total of 1,291 patients were included in the final analysis. BNP = B-type natriuretic peptide; D2F = door-to-furosemide; IV = intravenous; NT-proBNP = N-terminal pro-B-type natriuretic peptide; REALITY-AHF = Registry Focused on Very Early Presentation and Treatment in Emergency Department of Acute Heart Failure.

D2F time was non-normally distributed with a median value of 90 min (IQR: 36 to 186 min). Using a cutoff of 60 min, 481 patients (37.3%) were classified as the early treatment group and 810 (62.7%) composed the nonearly treatment group. Baseline characteristics for the groups are shown in Table 1. Patients in the early treatment group were more likely to arrive by ambulance; had acute onset of symptoms, higher blood pressure, and heart rate; and were more likely in sinus rhythm compared with those in the nonearly treatment group. Moreover, the early treatment group showed more signs of congestion, including higher New York Heart Association functional class and physical symptoms compared with the nonearly treatment group. Prescription of loop diuretics and aldosterone blocker before admission was more prevalent in the nonearly compared with the early treatment group.

Significant group differences in baseline laboratory markers were found for the white blood cell count and glucose level only. GWTG-HF risk score showed that the risk of the early treatment group was slightly lower than the nonearly treatment group. In terms of other treatments performed within 48 h, there were no significant group differences in the percentage of patients receiving catecholamines (dopamine, norepinephrine, or dobutamine): 16% in the early treatment group versus 15.5% in the nonearly treatment group ($p = 0.812$) or in the use of vasodilators (60.5% vs. 59.3%, respectively; $p = 0.681$). Because more patients in the nonearly treatment group had a history of HF and had received treatment with furosemide before admission, we separately evaluated group differences in the amount of oral diuretics taken within 48 h among patients with and without a history of HF. No significant group differences in the amount of diuretics taken during this period were found among those with (40 mg [IQR: 0 to 80 mg] vs. 40 mg [IQR: 20 to 80 mg]; $p = 0.124$) and without (0 mg [IQR: 0 to 30 mg] vs. 0 mg [IQR: 0 to 40 mg]; $p = 0.690$) a history of HF.

The results for the univariate and multivariable linear regression analyses predicting log-transformed D2F time are shown in Online Table 1 and Table 2, respectively. Arriving by ambulance and the presence of signs and symptoms of congestion, including orthopnea, jugular venous distension, angiotensin II receptor blocker prescription at admission, and a high heart rate, were independently associated with a shorter D2F time. In the final multivariable linear regression model, none of the individual covariate variance inflation factors was > 2 and the mean variance inflation factor across all covariates was 1.06.

TABLE 1 Baseline Characteristics

	Missing Data	Early Treatment Group (n = 481)	Nonearly Treatment Group (n = 810)	p Value
Age, yrs	0	79 ± 11	78 ± 13	0.391
Male	0	254 (53)	471 (58)	0.072
Arrived by ambulance	0	349 (73)	428 (53)	<0.001
Symptom onset time	0			<0.001
≤6 h		150 (31)	162 (20)	
6 h-2 days		103 (21)	179 (22)	
>2 days		228 (47)	469 (58)	
Systolic blood pressure, mm Hg	1 (0.1)	157 ± 37	147 ± 35	<0.001
Diastolic blood pressure, mm Hg	4 (0.3)	87 ± 26	83 ± 25	0.003
Heart rate, beats/min	0			
Total		102 ± 29	97 ± 28	0.001
Sinus patients		99 ± 22	93 ± 22	<0.001
AF patients		113 ± 32	105 ± 31	0.008
ECG rhythm	1 (0.1)			0.028
Sinus		286 (60)	419 (52)	
AF		155 (32)	307 (38)	
Others		40 (8)	83 (10)	
LVEF at ED	1 (0.1)			0.428
<35%		162 (37)	282 (37)	
35%-50%		144 (33)	222 (29)	
>50%		135 (30)	253 (34)	
NYHA III/IV at admission	1 (0.1)	426 (90)	632 (85)	0.012
Medical history				
Heart failure	0	225 (47)	428 (53)	0.038
Hypertension	0	342 (71)	539 (67)	0.095
Diabetes mellitus	0	180 (37)	294 (36)	0.720
Coronary artery disease	0	160 (33)	240 (30)	0.191
COPD	0	52 (11)	74 (9)	0.333
Current or ex-smoker	0	191 (40)	305 (38)	0.478
Physical findings at ED				
Peripheral edema	1 (0.1)	366 (76)	547 (68)	0.001
JVD	21 (1.6)	326 (69)	444 (56)	<0.001
Orthopnea	4 (0.3)	361 (75)	453 (56)	<0.001
Pulmonary edema	0	391 (81)	586 (72)	<0.001
Rale	2 (0.2)	370 (77)	522 (65)	<0.001

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D2F TIME AND IN-HOSPITAL MORTALITY. No patient was lost to follow-up for in-hospital outcome. During the index hospitalization, 11 patients (2.3%) in the early treatment group and 49 (6%) in the nonearly treatment group died (p = 0.002) (Figure 2). Although the mortality rate increased as GWTG-HF risk score increased in both groups (p for trend <0.05 for both groups), a lower mortality rate in the early treatment group compared with that for the nonearly treatment group was consistently observed across all quartiles, with the absolute risk difference increasing as GWTG-HF risk score quartile rose (p for trend = 0.027) (Figure 2). Table 3 shows the results of the univariate and multivariable logistic regression analyses. In logistic regression models, early treatment was associated with lower in-hospital mortality compared with nonearly treatment, even after adjustment for the GWTG-HF risk score. In GEE models, early treatment was associated with lower in-hospital mortality in univariate analysis (odds ratio [OR]: 0.36; 95% confidence interval [CI]: 0.21 to 0.62; p < 0.001) and after adjustment for the GWTG-HF risk score (OR: 0.42; 95% CI: 0.24 to 0.72; p < 0.001). In multivariable analysis, no significant interaction was seen between the early treatment group and GWTG-HF risk score on in-hospital mortality (p for interaction = 0.916). Additionally, there were no significant interactions between early treatment and any of the congestion symptoms (peripheral edema, jugular venous distension, orthopnea, pulmonary edema, and rales), arriving with ambulance or not, and sex (p for interaction >0.3 for all). The association between early treatment and in-hospital mortality did not differ significantly in patients with a history of HF (OR: 0.43; 95% CI: 0.19 to 1.00; p = 0.051) and without a history of HF (OR: 0.34; 95% CI: 0.11 to 1.03; p = 0.057) (p for interaction = 0.738).

As a sensitivity analysis, we constructed a logistic regression model and GEE model using D2F time as a continuous scale (log D2F time) with an adjustment for GWTG-HF risk score. In both models, the association between log D2F time and in-hospital mortality remained statistically significant (OR: 1.31; 95% CI: 1.04 to 1.64; p = 0.021 for the logistic regression model and OR: 1.31; 95% CI: 1.01 to 1.71; p = 0.045 for the GEE model). In the propensity score analysis, 708 patients were matched based on the propensity score. The baseline characteristics of the cohort after matching are shown in Online Table 2 and Online Figure 1. Among the matched patients, in-hospital mortality was, once again, lower in the early treatment group compared with that in the nonearly treatment group (5.9% vs. 2.5%; p = 0.038; OR: 0.41; 95% CI: 0.18 to 0.89; p value = 0.030). Furthermore, we tested the association between early treatment and 30-day mortality from the index hospitalization because there was variability in the length of hospital stay. In this additional sensitivity analysis, early treatment was associated with a lower 30-day mortality; however, the p value did not reach statistical significance in multivariable logistic regression analysis after adjusting for the GWTG-HF risk score or in the propensity score matching analysis (Table 3).

Figure 3 shows the association between D2F time and the probability of in-hospital mortality. Restricted cubic spline modeling with 4 knots was used because this model showed a better goodness-

of-fit compared with that for the linear model and restricted 3-knot cubic spline model ($p = 0.003$ and $p = 0.002$, respectively) and showed a comparable goodness-of-fit to the 5-knot model ($p = 0.579$). The association between D2F time and predicted in-hospital mortality was not linear, and predicted mortality steeply increased in the first approximately 100 min from ED arrival and leveled off afterwards.

DISCUSSION

A D2F time <60 min was observed in only one-third of patients with AHF who were hospitalized through the ED and treated with IV furosemide within 24 h. Patients with AHF presenting with more symptoms of congestion were more likely to be treated early. The association between D2F time and predicted in-hospital mortality had an inflection point; delaying D2F time steeply increased the mortality risk to the first approximately 100 min, but this effect leveled off thereafter (Central Illustration). D2F time <60 min was independently associated with a better in-hospital outcome.

D2F TIME AND PROGNOSTIC IMPLICATIONS. The present study showed that patients treated early were more likely to arrive by ambulance and had more prominent symptoms of congestion, consistent with previous studies performed in the ED setting (5,14). It is not surprising that the delivery of AHF treatment tended to be earlier in patients with more severe symptoms. Patients with symptoms and signs that were less obvious might have received the appropriate diagnosis at a later time point, and it is well known that the prompt and correct diagnosis of AHF in the ED remains challenging, especially for patients without a typical sign of congestion, because no historical or physical examination finding with adequately high sensitivity and specificity exists (15). Likewise, it is obvious that arrival by ambulance leads to early treatment given that these patients would be more symptomatic and/or caregivers more likely to start evaluating and treating them early from a logistics point of view. Females tended to be treated earlier than males. A recent post hoc analysis focused on dyspnea relief in the RELAX-AHF (Relaxin for the Treatment of Acute Heart Failure) study showed that female patients with AHF were more prone to dyspnea than men (16).

Several retrospective studies have previously evaluated the prognostic impact of early treatment in patients with AHF. In the ADHERE (Acute Decompensated Heart Failure National Registry), early treatment with nesiritide started in the ED was associated with a shorter mean hospital stay and less risk for a prolonged hospital stay (>7 days), but not with in-hospital mortality (17). However, because this analysis only included patients who were treated with nesiritide and excluded those treated with other vasodilators, the number of patients evaluated was narrowed from 105,388 to 4,300 (4.1%); thus, the

TABLE 1 Continued

	Missing Data	Early Treatment Group (n = 481)	Nonearly Treatment Group (n = 810)	p Value
Clinical profiles at ED	77 (6)			0.616
Warm-dry		12 (3)	28 (4)	
Warm-wet		391 (83)	594 (80)	
Cold-dry		54 (11)	92 (12)	
Cold-wet		16 (3)	27 (4)	
Medication at admission				
Loop diuretics	0	204 (42)	437 (54)	<0.001
ACE-I	5 (0.4)	78 (16)	141 (18)	0.592
ARB	4 (0.3)	159 (33)	243 (30)	0.291
Beta-blocker	8 (0.6)	190 (40)	341 (42)	0.379
Aldosterone blocker	1 (0.1)	86 (18)	192 (24)	0.014
Laboratory data				
WBC, /μl	0	8,200 (6,200–10,800)	7,400 (5,600–10,000)	<0.001
Hemoglobin, g/dl	0	11.5 (10.2–13.2)	11.7 (10.3–13.3)	0.512
AST, IU/l	1 (0.1)	32 (24–49)	31 (23–46)	0.833
ALT, IU/l	2 (0.2)	23 (14–35)	22 (14–36)	0.259
Creatinine, mg/dl	0	1.3 ± 0.9	1.4 ± 1.0	0.240
BUN, mg/dl	0	25 (18–33)	24 (18–35)	0.740
Glucose, mg/dl	51 (3.9)	181 ± 82	159 ± 73	<0.001
Sodium, mEq/l	1 (0.1)	139 ± 4	138 ± 5	0.452
CRP, mg/dl	3 (4)	0.64 (0.20–2.20)	0.73 (0.25–2.27)	0.396
BNP, pg/ml	126 (9.8)	737 (444–1,333)	746 (438–1,395)	0.836
Length of hospital stay, days	0	17 (11–26)	17 (11–26)	0.457
GWTG-HF risk score	1 (0.1)	37 ± 8	38 ± 8	0.028

Values are mean ± SD, n (%), or median (interquartile range).

ACE-I = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ALT = aspartate aminotransferase; ARB = angiotensin II receptor blocker; AST = alanine aminotransferase; BNP = B-type natriuretic peptide; BUN = blood urea nitrogen; COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; ECG = electrocardiogram; ED = emergency department; GWTG-HF = Get With the Guidelines-Heart Failure; JVD = jugular venous distention; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; WBC = white blood cell.

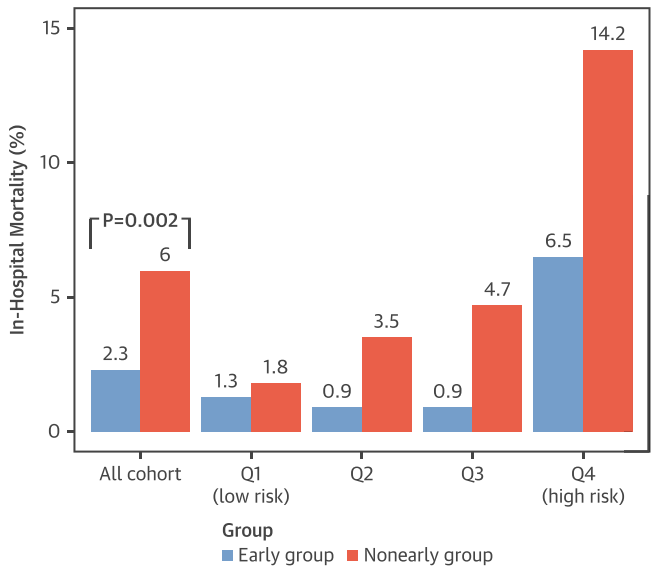
TABLE 2 Log-Transformed Door-to-Furosemide Time

	B Coefficient*	Standardized Beta*	t Value*	p Value
Orthopnea	−0.455	−0.178	−6.278	<0.001
Arrived by ambulance	−0.323	−0.128	−4.646	<0.001
JVD	−0.307	−0.121	−4.371	<0.001
Heart rate	−0.003	−0.077	−2.781	0.006
Male	0.137	0.055	2.055	0.040
ARB at admission	−0.143	−0.054	−1.979	0.048

*A factor with a negative coefficient is associated with an earlier administration of intravenous furosemide.

Abbreviations as in Table 1.

FIGURE 2 In-Hospital Mortality



Early treatment resulted in lower mortality overall and stratified by quartiles (Q) of Get with the Guidelines-Heart Failure Score. In-hospital mortality was significantly lower in early treatment group compared to nonearly treatment group (2.3% vs. 6%; p = 0.002). Early treatment groups consistently showed a lower mortality rate compared with that for the nonearly treatment group across all quartiles, with the absolute risk difference increasing as the Get With the Guidelines-Heart Failure risk score quartile rose.

generalizability of these results to all patients with AHF is unclear. Moreover, the use of other IV drugs, such as IV diuretics, was not taken into account in ADHERE, despite the fact that more than 95% of the patients were treated with IV diuretics, predominantly furosemide.

In another study using ADHERE data, an association between the time to administration of the first vasoactive agent and in-hospital mortality was evaluated in patients who received an IV vasoactive agent (nesiritide, nitroglycerin, nitroprusside, dobutamine, dopamine, or milrinone) (6). In this study, a shorter time to the first vasoactive agent was associated with better in-hospital mortality. This might support the results of the present study; however, early treatment in the previous study was defined as the use of an IV vasoactive agent ≤6 h from hospitalization (not ED arrival). Because the time to hospitalization varies widely as a result of the many factors involved, it is difficult to draw a conclusion regarding the beneficial impact of early treatment from this study. Also, similar to the aforementioned ADHERE study, only 25% of all initially registered patients were treated with IV vasoactive agents and were included in the study. Thus, selection biases might have existed and the generalizability of the findings is unknown.

TABLE 3 Logistic Regression Analysis*

	In-Hospital Mortality			30-Day Mortality		
Adjustment	**OR**	**95% CI**	**p Value**	**OR**	**95% CI**	**p Value**
Univariate	0.36	0.19–0.71	0.002	0.52	0.28–0.96	0.037
Adjusted for GWTG-HF risk score	0.39	0.20–0.76	0.006	0.56	0.13–1.0	0.072
Propensity score matching	0.41	0.18–0.89	0.030	0.49	0.22–1.05	0.067

*Table includes univariate and multivariable logistic regression models for in-hospital mortality comparing the early with the nonearly treatment group.

CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

The ADHERE-EM (emergency module) dataset is a retrospective study evaluating patients with AHF who presented at the ED. The prognostic implication of the time from ED admission to the first IV HF therapy administration (loop diuretics, inotropes, or vasodilators, whichever was administered first) was evaluated in 6,971 patients with AHF age ≥65 years registered in this dataset (14). Results showed that a delay in treatment was independently associated with a modest but significant increase in the risk of in-hospital mortality when time to treatment was examined as a continuous variable. Likewise, Maisel et al. (5) retrospectively evaluated the association between time to first IV furosemide and in-hospital mortality in patients with AHF hospitalized via the ED using ADHERE registry data. The authors demonstrated that in-hospital mortality increased by 2.1% per every 4 h of delay in the time to first IV furosemide.

In contrast to previous studies, REALITY-AHF was a prospective study, specifically designed to examine the association between time to treatment and clinical outcome. One of the novel and interesting findings obtained from the present study was that the association between D2F time and in-hospital mortality might not be linear. In the first few hours after ED arrival, mortality steeply increased as D2F time was delayed, but this effect leveled off after approximately 100 min. These findings might support the currently recommended time window of 30 to 60 min after ED arrival for the initiation of management for patients with AHF (8). It might also suggest that if physicians are more confident of the definite diagnosis of HF (more HF signs and symptoms), treatment with loop diuretics is commenced earlier and might be associated with better outcomes. Furthermore, no interaction between the prognostic impact of early treatment and baseline risk was found, and this treatment strategy might be even more effective in high-risk patients with AHF. Nonetheless, the present study and analysis could not determine the optimal

D2F time, which needs to be evaluated in a future study.

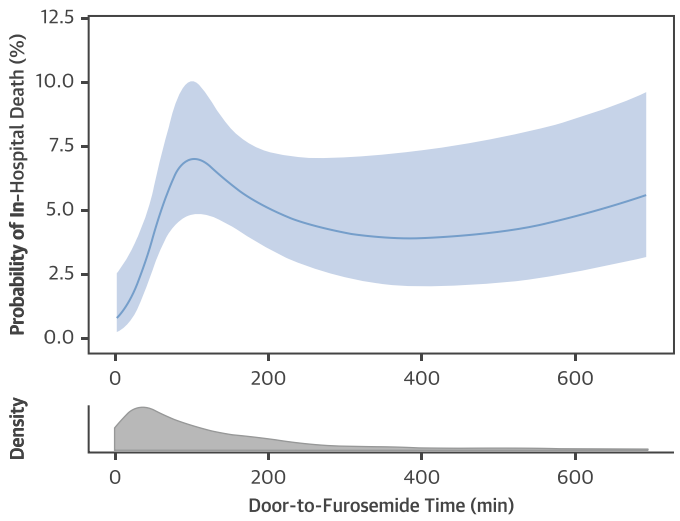
The present study was not designed to provide a clear explanation regarding the pathophysiological mechanism underlying the association between D2F time and in-hospital outcomes. However, a recent substudy of RELAX-AHF evaluated biomarker trajectories and showed that some organ damage markers (including high-sensitivity troponin) increased over time in the first 2 days in placebo groups; this increase was associated with mortality (18). Moreover, early treatment with serelaxin significantly attenuated the increase in high-sensitivity troponin within 2 days and decreased mortality. These results imply that myocardial damage is a progressive phenomenon in the acute phase among patients with AHF, and that early treatment mitigating this organ damage might consequently improve outcomes. Because we did not collect serial troponin data in the present study, this hypothesis should be evaluated in a future study.

The present study findings may have an implication on both clinical practice and future clinical studies for patients with AHF. Previous major AHF clinical studies have not paid much attention to time to treatment and they consequently failed to recruit patients in the early phase of AHF (1). Although the Trial of Ularitide Efficacy and Safety in Acute Heart Failure did not show positive results (19), despite recruitment of patients in the relatively early phase, the time from presentation to initiation of treatment appeared to be one of the most important factors to take into account in future clinical studies on AHF.

STUDY LIMITATIONS. All previous analyses regarding an association between early treatment and prognosis have been derived from only 1 dataset (ADHERE), which retrospectively registered hospitalized patients with HF without a focus on the time-to-treatment concept. The present study, for the first time, prospectively focused on this concept in patients with AHF. Given that we used D2F time as a metric of early treatment, our study results have wide applicability for patients with AHF because a substantial proportion requires IV furosemide in the acute phase.

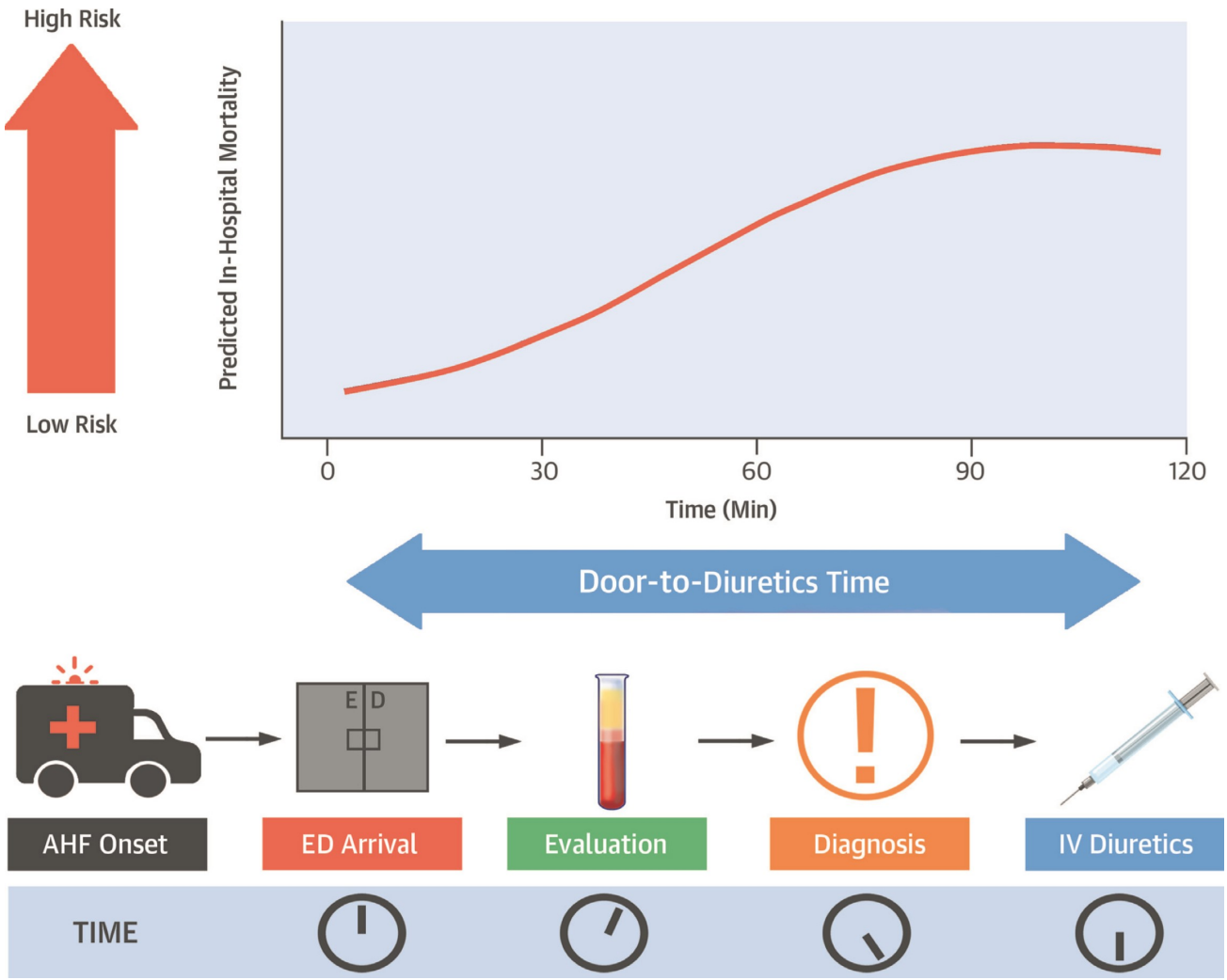
The small number of events in our study might lead to the risk of type I error, and study results need to be replicated in future studies. We did not collect data regarding time to laboratory data or time to BNP or NT-proBNP measurement; thus, it is difficult to discriminate between time to diagnosis and time to treatment. Therefore, even with these data, it remains difficult to clearly define the exact time of diagnosis. We do not have data on the respiratory rate or cause of HF exacerbation, which might have an impact on outcomes. Also, an association between D2F time and long-term prognosis should be evaluated in a future study. In Japan, the median length of hospital stay is substantially longer than that for Western countries, which might affect the study results, especially for in-hospital mortality. However, in-hospital mortality was not substantially different between our study cohort and other registries representing American and European patients with AHF (4.0% in ADHERE and 6.7% in EuroHeart Survey II) (20,21). Moreover, we obtained a similar association between early treatment and 30-day mortality from the time of the index admission. Because differences in ED systems potentially exist between institutions, our study results might not apply to all institutions. We attempted to adjust for confounders as much as possible by using a risk score that has been validated in Japanese patients with AHF, and showed consistency of our results in sensitivity analyses. Nevertheless, we agree with the possibility that a potential unadjusted confounding could remain, such as a "confounding by indication." Therefore, our study results should be interpreted carefully because there is a considerable possibility that residual confounders remain because

FIGURE 3 Probability Plot for In-Hospital Mortality



The **solid blue line** represents the estimated probability of in-hospital mortality, the **light blue shaded area** is 95% confidence interval, and the **gray shaded area** is a density plot showing the distribution of observed door-to-furosemide time.

CENTRAL ILLUSTRATION **Door-to-Diuretics Time and In-Hospital Mortality**



Matsue, Y. et al. J Am Coll Cardiol. 2017;69(25):3042–51.

Door-to-diuretics time consists of the time needed to perform evaluation, make a diagnosis, and start intravenous (IV) diuretic therapy after patients with acute heart failure (AHF) arrive at the emergency department (ED). This study showed that mortality increased as the door-to-diuretics time was delayed.

there were many differences in patient background between the early and nonearly groups. It should also be noted that D2F time may be associated with prognosis through its association with interinstitutional differences in quality of care for patients with AHF in the ED rather than any direct association with prognosis, although we showed a consistent result in the model accounting for it. Moreover, given its observational nature, it should be noted that only an association, not causality, was demonstrated in the present study.

These limitations clearly indicate that our study results are only hypothesis-generating; however, it is virtually impossible to randomize patients to a delayed-treatment group from an ethical point of view. Because we included only patients hospitalized through the ED, the applicability of our study results to nonhospitalized patients is unclear. Additionally, we included only patients who were treated with IV furosemide within 24 h without any scientific basis for this time limit. However, recent studies regarding in-hospital worsening

HF used 24 h from admission as the end of the acute phase (22,23). Moreover, changing the time window for patient inclusion from 24 to 48 h did not change our results substantially (data not shown).

CONCLUSIONS

In a prospective observational study focused on the acute phase in the management of patients with AHF, we demonstrated that patients with AHF and prominent congestive symptoms were more likely to be treated early with IV furosemide. Furthermore, treatment with IV furosemide within 60 min was independently associated with better in-hospital survival.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients hospitalized with AHF, delayed treatment with intravenous furosemide was associated with increased mortality.

TRANSLATIONAL OUTLOOK: Long-term follow-up studies are needed to better understand the impact of early diuretic treatment on outcomes in patients with HF.

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KEY WORDS B-type natriuretic peptide, diuretics, emergency department, Get With the Guidelines, prognosis

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