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CLINICAL RESEARCH

The Effect of Door-to-Diuretic Time on Clinical Outcomes in Patients With Acute Heart Failure

Jin Joo Park, MD,[a] Sun-Hwa Kim, PhD,[a] Il-Young Oh, MD,[a] Dong-Ju Choi, MD,[a] Hyun-Ah Park, MD,[b] Hyun-Jai Cho, MD,[c] Hae-Young Lee, MD,[c] Jae-Yeong Cho, MD,[d] Kye Hun Kim, MD,[d] Jung-Woo Son, MD,[e] Byung-Su Yoo, MD,[e] Jaewon Oh, MD,[f] Seok-Min Kang, MD,[f] Sang Hong Baek, MD,[g] Ga Yeon Lee, MD,[h] Jin Oh Choi, MD,[h] Eun-Seok Jeon, MD,[h] Sang Eun Lee, MD,[i] Jae-Joong Kim, MD,[i] Ju-Hee Lee, MD,[j] Myeong-Chan Cho, MD,[j] Se Yong Jang, MD,[k] Shung Chull Chae, MD,[k] Byung-Hee Oh, MD[c]

ABSTRACT

OBJECTIVES This study sought to examine the impact of door-to-diuretic (D2D) time on mortality in patients with acute heart failure (AHF) who were presenting to an emergency department (ED).

BACKGROUND Most patients with AHF present with congestion. Early decongestion with diuretic agents could improve their clinical outcomes.

METHODS The Korea Acute Heart Failure registry enrolled 5,625 consecutive patients hospitalized for AHF. For this analysis, the study included patients who received intravenous diuretic agents within 24 h after ED arrival. Early and delayed groups were defined as D2D time ≤60 min and D2D time >60 min, respectively. The primary outcomes were in-hospital death and post-discharge death at 1 month and 1 year on the basis of D2D time.

RESULTS A total of 2,761 patients met the inclusion criteria. The median D2D time was 128 min (interquartile range: 63 to 243 min), and 663 (24%) patients belonged to the early group. The baseline characteristics were similar between the groups. The rate of in-hospital death did not differ between the groups (5.0% vs. 5.1%; $p > 0.999$), nor did the post-discharge 1-month (4.0% vs. 3.0%; log-rank $p = 0.246$) and 1-year (20.6% vs. 19.3%; log-rank $p = 0.458$) mortality rates. Get With the Guidelines-Heart Failure risk score was calculated for each patient. In multivariate analyses with adjustment for Get With the Guidelines-Heart Failure risk score and other significant clinical covariates and propensity-matched analyses, D2D time was not associated with clinical outcomes.

CONCLUSIONS The D2D time was not associated with clinical outcomes in a large prospective cohort of patients with AHF who were presenting to an ED. (Registry [Prospective Cohort] for Heart Failure in Korea [KorAHF]; NCT01389843) (J Am Coll Cardiol HF 2018;6:286–94) © 2018 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]Cardiovascular Center, Division of Cardiology, Seoul National University Bundang Hospital, Seongnam, Republic of Korea; [b]Department of Family Medicine, Inje University Seoul Paik Hospital, Seoul, Republic of Korea; [c]Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea; [d]Heart Research Center of Chonnam National University, Gwangju, Republic of Korea; [e]Yonsei University Wonju College of Medicine, Wonju, Republic of Korea; [f]Yonsei University College of Medicine, Seoul, Republic of Korea; [g]Department of Internal Medicine, the Catholic University of Korea, Seoul, Republic of Korea; [h]Department of Internal Medicine, Sungkyunkwan University College of Medicine, Seoul, Republic of Korea; [i]Division of Cardiology, Asan Medical Center, Seoul, Republic of Korea; [j]Chungbuk National University College of Medicine, Cheongju, Republic of Korea; and the [k]Kyungpook National University College of Medicine, Daegu, Republic of Korea. This work was supported by Research of Korea Centers for Disease Control and Prevention (grant nos. 2010-E63003-00, 2011-E63002-00, 2012-E63005-00, 2013-E63003-00, 2013-E63003-01, 2013-E63003-02, and 2016-ER6303-00) and by the SNUBH Research Fund (grant nos. 14-2015-029, 16-2017-003). All authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Acute heart failure (AHF) is a life-threatening condition with high morbidity and mortality, which requires immediate medical intervention (1). Most patients with AHF present with signs and symptoms of congestion, but few present with symptoms of low cardiac output (2). Thus, early decongestion with diuretic agents is 1 of the cornerstones for the treatment for patients with AHF (1).

In patients with ST-segment elevation myocardial infarction (STEMI), the door-to-balloon time correlates with the extent of myocardial injury and patients' outcomes (3,4); accordingly, the current practice guideline recommends a door-to-balloon time of <90 min (5). Similarly, the concept of "time to therapy" has been introduced in patients with AHF, by emphasizing the rapid initiation of diagnosis and therapeutic intervention. Recently, Matsue et al. (6) reported that patients with AHF receiving intravenous loop diuretic agents within 60 min after emergency department (ED) arrival had lower in-hospital mortality rates.

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In contrast to patients with STEMI, where acute occlusion of a coronary artery and the following ischemia lead to irreversible myocardial injury within a short time period ("time is myocardium"), AHF is a "subacute" process with a remote trigger and successive decompensation leading to hemodynamic and clinical congestion. Considering the reversibility of congestion and the relatively long time period between the trigger and full-blown AHF, the door-to-diuretic (D2D) time may have limited clinical impact on clinical outcomes.

In this study, we sought to examine the effect of D2D time on the in-hospital and post-discharge clinical outcomes in a large, prospective cohort of patients with AHF presenting to an ED.

ABBREVIATIONS AND ACRONYMS

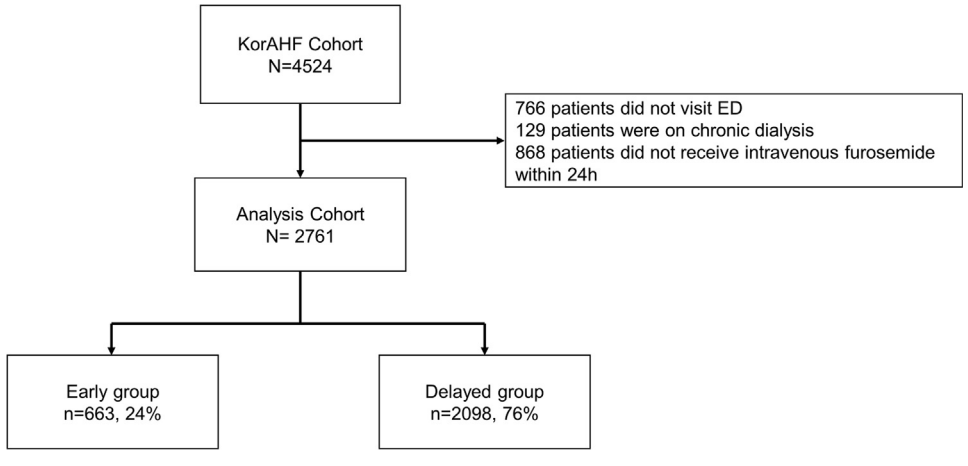
AHF = acute heart failure
D2D = door-to-diuretic
ED = emergency department
EF = ejection fraction
GWTG-HF = Get With the Guidelines-Heart Failure
HF = heart failure
NYHA = New York Heart Association
STEMI = ST-segment elevation myocardial infarction

METHODS

PATIENTS. The Korea Acute Heart Failure (KorAHF) registry was a prospective, multicenter cohort study that consecutively enrolled 5,625 patients hospitalized for AHF syndrome from 10 well-known tertiary university hospitals throughout Korea between March 2011 and December 2014 (NCT01389843). Detailed information on the study design and its results have been previously reported (7,8). Patients with signs or symptoms of heart failure (HF) and lung congestion, objective findings of left ventricular systolic dysfunction, or structural heart disease were eligible for the study. All patients were scheduled for follow-up at least 3 years after the index hospitalization. The mortality data for patients who were lost to follow-up were collected from the National Insurance data or National Death Records.

In this study, we included only patients who were admitted to an ED and received intravenous furosemide within 24 h after ED arrival. Patients who received the first dose of furosemide 24 h after ED arrival were excluded because they may have received

FIGURE 1 Study Population



ED = emergency department; KorAHF = Korea Acute Heart Failure.

TABLE 1 Baseline Characteristics of the Study Population

	Early Group n = 663 (24%)	Delayed Group n = 2,098 (76%)	p Value
Age, yrs	70.1 ± 13.5	70.6 ± 14.0	0.397
Men	47.8	49.3	0.495
De novo	54.0	55.6	0.463
Body mass index, kg/m^2	23.2 ± 3.7	23.2 ± 3.9	0.776
Past medical history			
Hypertension	62.6	61.9	0.737
Diabetes mellitus	38.9	35.8	0.152
Chronic kidney disease*	49.8	46.7	0.169
Ischemic heart disease	33.5	27.6	0.004
Valvular heart disease	10.7	13.4	0.070
Atrial fibrillation	23.4	28.8	0.006
COPD	9.0	12.1	0.033
Cerebrovascular disease	14.8	15.4	0.698
Malignancy	7.1	7.5	0.705
Current smoking	20.1	16.8	0.053
ICD	1.4	1.0	0.440
CRT	0	0.5	0.062
NYHA functional class			<0.001
II	9.5	9.9	
III	23.5	34.2	
IV	67.0	55.9	
Physical examination (at admission)			
Systolic BP, mm Hg	141.1 ± 34.1	135.9 ± 30.0	<0.001
Diastolic BP, mm Hg	84.5 ± 20.2	81.1 ± 18.9	<0.001
Heart rate, beats/min	100.5 ± 27.6	95.3 ± 25.4	<0.001
Lung congestion	89.7	86.5	0.027
Laboratory findings			
Hemoglobin, mg/dl	12.3 ± 2.3	12.2 ± 2.2	0.275
Serum sodium, mmol/l	137.3 ± 4.9	137.2 ± 4.7	0.561
Serum potassium, mmol/l	4.4 ± 0.8	4.4 ± 0.7	0.238
BUN, mg/dl	25.1 ± 15.9	26.1 ± 15.7	0.157
Creatinine, mg/dl	1.41 ± 1.10	1.39 ± 1.17	0.694
BNP, pg/ml	1,497 ± 1,356	1,409 ± 1,234	0.289
NT-proBNP, pg/ml	9,290 ± 9,658	10,354 ± 11,055	0.095
Troponin I, ng/ml	1.48 ± 5.65	1.95 ± 11.16	0.330
Troponin T, ng/ml	0.23 ± 1.10	0.18 ± 0.57	0.674
C-reactive protein	2.6 ± 4.5	2.5 ± 3.4	0.599
Echocardiographic parameters			
LVEF	37.2 ± 14.8	38.4 ± 15.7	0.087
HF type			0.086
HFpEF	62.7	58.7	
HFmrEF	14.7	14.2	
HFpEF	22.5	27.1	
Medications at admission			
RAS inhibitor	37.4	36.9	0.811
BB	29.9	28.0	0.348
MRA	15.7	16.7	0.528

Continued on the next page

intravenous furosemide for worsening HF during the hospital admission. We also excluded patients who were undergoing long-term dialysis therapy before hospital admission and patients who received oral furosemide in ED. The study protocol was approved by the ethics committee or Institutional Review Board at each hospital. Written informed consent was waived by the ethics committee or Institutional Review Board. The study complied with the Declaration of Helsinki.

STUDY VARIABLES AND DEFINITIONS. The ED arrival time and intravenous furosemide administration time were documented for each patient, and the D2D time was defined as the time interval between ED arrival and the first intravenous administration of furosemide. Early and delayed treatment groups were defined as D2D time <60 min and ≥60 min, respectively. The cutoff time of 60 min was decided on the basis of earlier reports, which concluded that a D2D time <60 min was reported to be associated with a 61% lower in-hospital mortality rate (6). The primary outcomes were the rates of in-hospital death and 1-month and 1-year post-discharge all-cause death. Secondary outcomes included the use of catecholamines, mechanical circulatory support devices, and mechanical ventilation.

We planned 4 exploratory subgroup analyses according to the following: 1) ejection fraction (EF); 2) HF onset (de novo vs. acute decompensation); 3) renal function (chronic kidney disease vs. no chronic kidney disease); and 4) New York Heart Association (NYHA) functional class (II to III vs. IV). Patients were classified as having HF with reduced, midrange, and preserved EF with a left ventricular ejection fraction cutoff of 40% and 50%, respectively. Chronic kidney disease was defined as an initial glomerular filtration rate <60 ml/min/1.72 m^2.

STATISTICAL ANALYSIS. A sample size of 2,750 (650 in the early group and 2,100 in the delayed group) would achieve a 90% power to detect a difference between the group proportions of 4%. The in-hospital death rate in the early group is assumed to be 2% (6). The test statistic used is the 2-sided z-test with pooled variance. The significance level of the test was targeted at 5%.

Data are presented as numbers and frequencies for categorical variables and as mean ± SD or median with interquartile ranges for continuous variables. For comparisons among groups, the chi-square test (or the Fisher exact test when any expected count was <5 for a 2 × 2 table) was used for categorical variables, and the unpaired Student's t-test or Mann-Whitney U test was used for continuous variables.

The Get With the Guidelines-Heart Failure (GWTG-HF) score was calculated for each patient (9) and was used for estimation of risk. Kaplan-Meier curves were plotted and compared, using the log-rank test for evaluation of post-discharge outcomes. A multivariable logistic regression and Cox proportional hazards regression models were used to determine the independent effect of D2D time on in-hospital and

post-discharge outcomes, respectively. Variables found to be statistically significant ($p < 0.10$) in the univariate analysis were included in the multivariable model, except for variables with >10% missing values or variables that were closely related to other clinical variables. As a sensitivity analysis, we developed models with adjustment with GWTG-HF score and propensity score matching. Propensity score matching was done for comparisons between the 2 groups (early group vs. delayed group). The propensity score was estimated using multivariable logistic regression analysis with the variables listed in the second adjustment model. A propensity score-matched cohort was created using the nearest neighbor method without replacement, in a 1:2 ratio. The "MatchIt" package of R programming (The R Foundation for Statistical Computing, Vienna, Austria) was used for the matching.

A 2-sided probability value <0.05 was considered indicative of a statistically significant difference. Statistical tests were performed using SPSS software version V.22 (IBM, Armonk, New York), R programming version 3.1.0, and PASS 11 (NCSS, LLC, Kaysville, Utah). All the analyses were performed by a professional statistician (S.-H.K.).

TABLE 1 Continued

	Early Group n = 663 (24%)	Delayed Group n = 2,098 (76%)	p Value
Medications at discharge			
RAS inhibitor	69.4	67.5	0.376
BB	53.7	50.3	0.131
MRA	46.6	43.2	0.122
GWTG-HF Score	40.5 ± 8.2	41.2 ± 7.8	0.058
GWTG-Quartiles			0.016
Q1	33.5	27.1	
Q2	22.9	25.6	
Q3	20.9	22.6	
Q4	22.6	24.7	

Values are % or mean ± SD, unless otherwise indicated. *Chronic kidney disease was defined as a glomerular filtration rate <60 ml/min/1.72 m^2.

BB = beta-blocker; BP = blood pressure; BUN = blood urea nitrogen; BNP = B-type natriuretic peptide; COPD = chronic obstructive pulmonary disease; CRT = cardiac resynchronization therapy; GWTG-HF = Get With the Guidelines-Heart Failure; HFpEF = heart failure with preserved ejection fraction; HFmrEF = HF with midrange EF; HFrEF = HF with reduced EF; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; NT-proBNP = N-terminal pro-B-type natriuretic peptide; Q = quartile; RAS = renin-angiotensin system.

RESULTS

PATIENTS. The KorAHF registry included 5,625 patients at 10 tertiary academic centers in Korea. In this study, 8 centers with 4,524 patients participated. Of them, 766 patients did not visit an ED, 129 were undergoing long-term dialysis, and 868 did not receive intravenous furosemide within 24 h, so the data of 2,761 patients were available for the final analysis (Figure 1). The mean age was 70 years, 49% were male, 55% had de novo HF, 37% had diabetes, and 62% had hypertension.

The D2D time was non-nominally distributed with a median of 128 min (interquartile range: 63 to 243 min). According to the definition, 663 (24%) patients were classified as belonging in the early group and 2,098 (76%) were classified as belonging in the delayed group. The baseline characteristics were similar between the groups, except that patients in the early group had higher mean blood pressure, whereas those in the delayed group had a higher rate of atrial fibrillation. More NYHA functional class IV patients were in the early group, whereas patients in the delayed group had higher GWTG-HF scores with a marginal significance ($p = 0.058$) (Table 1). In a logistic regression analysis, the presence of atrial fibrillation and COPD and a higher GWTG score were independently associated with delayed D2D time, whereas ischemic heart disease, advanced NYHA functional class, and a higher heart rate were associated with early D2D time. The participating center was not associated with D2D time (Table 2).

IN-HOSPITAL OUTCOMES. Regarding intravenous catecholamine and vasodilator use, there was no difference between the groups. Patients in the early group required mechanical ventilation more often (19% vs. 13%; $p < 0.001$) than those in the delayed group (Table 3).

During hospital admission, 140 (5.1%) patients died. The rate of in-hospital mortality did not differ between the groups (Figure 2). When stratified according to the GWTG-HF score, the in-hospital death rate increased with GWTG-HF score tertiles, but without significant difference between the early and delayed groups (Online Table 1).

On logistic regression analysis, delayed treatment was not associated with in-hospital death in univariate analysis (odds ratio: 1.03; 95% confidence interval: 0.69 to 1.53), after adjustment for GWTG-HF score (odds ratio: 1.00; 95% confidence interval: 0.66 to 1.52) and significant covariates (odds ratio: 1.05; 95% confidence interval: 0.64 to 1.70) (Table 4).

POST-DISCHARGE OUTCOMES. During follow-up after hospital discharge, 85 (3.1%) patients died at 1 month, and 514 (18.6%) patients at 1 year. In Kaplan-Meier survival curves, the rates of post-discharge 1-year all-cause death and hospitalization for worsening HF did not differ between the groups (Figures 3A and 3B).

TABLE 2 Predictors of Delayed D2D Time*

	p-Value	Odds Ratio	95% CI
Ischemic heart disease	0.004	0.74	0.60–0.91
Atrial fibrillation	0.017	1.31	1.05–1.64
COPD	0.033	1.43	1.03–1.98
NYHA	<0.001	0.76	0.65–0.88
Heart rate	<0.001	0.99	0.98–0.99
GWTG Score	0.030	1.01	1.00–1.03

*Binary logistic regression with forward conditional modeling (delayed group as outcome variable): included variables were age, sex, and those with $p < 0.10$ in univariate analysis. Variables included in the multivariable analyses were sex, age, ischemic heart disease, atrial fibrillation, previous valvular heart disease, COPD, current smoker, CRT implantation, NYHA functional class, systolic blood pressure (mm Hg), heart rate, lung congestion on radiography, LVEF, and GWTG-HF Score, and institution name.

CI = confidence interval; D2D = door-to-diuretic; GWTG = Get With the Guidelines; other abbreviations as in Table 1.

TABLE 3 Clinical Outcomes

	Early Group n = 663 (24%)	Delayed Group n = 2,098 (76%)	p Value
Inotrope use	32.7	27.6	0.012
Intravenous vasodilator	47.4	55.6	<0.001
Mechanical ventilator	19.0	12.9	<0.001
Duration, days	6.8 ± 11.5	7.3 ± 10.9	0.677
MCSD	5.6	5.1	0.628
IABP	4.7	3.5	0.158
ECMO	1.7	2.0	0.527
CRRT	0.3	0.6	0.393
WRF	60.0	57.0	0.163
Improved WRF	60.6	62.0	0.900
In-hospital outcomes			
In-hospital death	5.0	5.1	>0.999
Lengths of stay, days	13.4 ± 14.7	13.0 ± 14.0	0.478
Post-discharge outcomes			
30-day all-cause death	4.0	3.0	0.238
30-day HHF	7.1	6.9	0.822
30-day death + HHF	10.8	9.7	0.422
1-yr all-cause death	20.6	19.3	0.458
1-yr HHF	22.1	21.8	0.888
1-yr death + HHF	36.3	35.3	0.618

Values are % or mean ± SD.

CRRT = continuous renal replacement therapy; ECMO = extracorporeal membrane oxygenation; HHF = hospitalization for heart failure; IABP = intra-aortic balloon pump; MCSD = mechanical circulatory support device; WRF = worsening renal function.

Delayed treatment was not associated with worse outcomes in univariate analysis, after adjustment for GWTG-HF score, and in multivariable analysis (Table 4).

PROPENSITY-MATCHED COHORT. A total of 1,959 patients were matched on the basis of the propensity score. The baseline characteristics of the cohort after matching were well balanced (Online Table 2). In the matched population, the rate of in-hospital mortality and the post-discharge 1-month and 1-year mortality rates did not differ between the early and delayed groups (Online Figures 1A and 1B).

SUBGROUP ANALYSIS. We performed 4 exploratory subgroup analyses including left ventricular EF, HF onset, renal function, and NYHA functional class. There was no significant interaction between D2D time and the subgroups, and D2D time was not associated with in-hospital and post-discharge outcomes across all subgroups (Online Figure 2).

RELATIONSHIP BETWEEN D2D TIME AND IN-HOSPITAL MORTALITY RATE. Most patients received intravenous diuretic agents within 200 min, and the number of patients with D2D time >200 min decreased rapidly. In a restricted cubic spline modeling with 4 knots, the association between D2D time and predicted in-hospital mortality rate was not linear; there seems to be an initial decrease in the first 100 min, followed by a gradual increase afterward. However, because of the wide confidence interval, a clear association cannot be made (Figure 4).

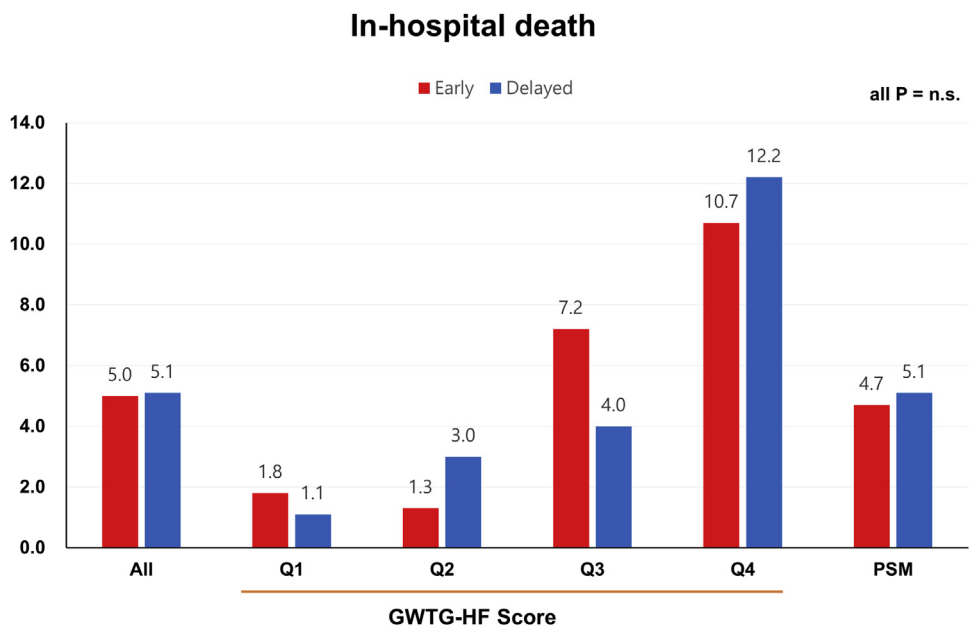
DISCUSSION

Akin to treatment of acute myocardial infarction, the concept of "time to therapy" has also been introduced in patients with AHF, by emphasizing the rapid initiation of diagnosis and therapeutic intervention. Because most patients with AHF present with congestion, current AHF treatment guidelines also advocate the timely initiation of diuretic therapy (2). Early decongestion improves symptoms and possibly patients' survival (6). In this study of a large prospective cohort of patients with AHF presenting to EDs, we examined the impact of D2D time on outcomes, and showed that D2D time was not associated with either in-hospital or post-discharge outcomes.

D2D time varied notably among patients with a median of 128 min and an interquartile range of 63 to 243 min. Because this was not a randomized controlled study, but rather a prospective cohort study, the observed D2D time reflected real clinical practice: the time to diagnosis of HF and the time to the decision to initiate diuretic agents varied considerably from patient to patient.

A total of 24% of the patients received intravenous diuretic agents within 60 min after ED arrival. Although the baseline characteristics were similar between the groups, patients in the early group had more NYHA functional class IV dyspnea and lung congestion visible on chest radiography, as expected. Symptoms indicative of advanced congestion may have alerted the clinicians to earlier diagnosis and

FIGURE 2 Clinical Outcomes



The in-hospital death rate did not differ between patients in the early and delayed groups in all, and across the quartiles (Q1 to Q4) of the Get With the Guidelines-Heart Failure (GWTG-HF) score, and propensity score–matched (PSM) population. All p values for the group difference between the early and delayed groups were insignificant across all stratifications.

initiation of diuretic agents. However, patients in the early group also had more favorable risk profiles such as higher blood pressure and lower GWTG-HF score than those in the delayed group, with a marginal significance.

The main finding of this study was that there was no difference in the in-hospital and post-discharge outcomes between patients in the early and delayed groups. The neutral association between D2D and the clinical outcomes was consistent in the univariate and multivariate analyses with adjustment for GWTG-HF score and significant clinical covariates, as well as in the propensity score–matched analysis. Our study findings contradict those of Matsue et al. (6), who reported that D2D time <60 min was associated with a 61% reduced risk for in-hospital mortality in 1,291 patients with AHF presenting at ED in Japan. Although there are differences in patients' characteristics between the 2 studies, this finding is significant because the study populations of both studies were East Asians with comparable risk profiles (Online Table 3).

The concept of "time to therapy" in patients with AHF includes the timely initiation of diuretic therapy, inferring from the experiences in patients with acute myocardial infarction who benefit from early recanalization therapy. Although both "acute" myocardial infarction and "acute" HF seem to be "acute" processes, there are important differences in the pathophysiologic aspects. In patients with STEMI, sudden occlusion of a coronary artery is the trigger that causes ischemia and myocardial cell deaths, which begin instantly ("time is myocardium") (10). Rapid reperfusion, which specifically targets the underlying pathophysiology, preserves the myocardium and heart function and consequently improves the prognosis. In contrast, AHF is a heterogeneous disease, which is a syndrome rather than a single disease entity with various triggers (e.g., infection or noncompliance), followed by successive hemodynamic and clinical congestion. Adamson et al. (11), using an implantable hemodynamic monitor, showed that the pressure increases 4 days before the exacerbations requiring hospitalization in patients with HF. Similarly, in the CHAMPION (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients) study, the daily measurement of pulmonary artery pressures and adjustment of medication with diuretic agents and vasodilators reduced the rehospitalization rate, thus demonstrating the *subacute* nature of AHF (12).

TABLE 4 Impact of D2D Time on Clinical Outcomes

	p Value	Exp (Beta)	95% CI
In-hospital death			
Univariate	0.900	1.03	0.69-1.53
Adjustment for GWTG-HF score	0.989	1.00	0.66-1.52
Adjustment for significant covariates*	0.861	1.05	0.64-1.70
Propensity score–matched cohort	0.714	1.09	0.70-1.68
Post-discharge 1-month AC death			
Univariate	0.248	0.76	0.48-1.21
Adjustment for GWTG-HF score	0.157	0.71	0.45-1.14
Adjustment for significant covariates†	0.201	0.73	0.45-1.19
Propensity score–matched cohort	0.077	0.62	0.37-1.05
Post-discharge 1-yr AC death			
Univariate	0.458	0.93	0.76-1.13
Adjustment for GWTG-HF score	0.221	0.88	0.72-1.08
Adjustment for significant covariates†	0.110	0.84	0.68-1.04
Propensity score–matched cohort	0.102	0.83	0.67-1.04

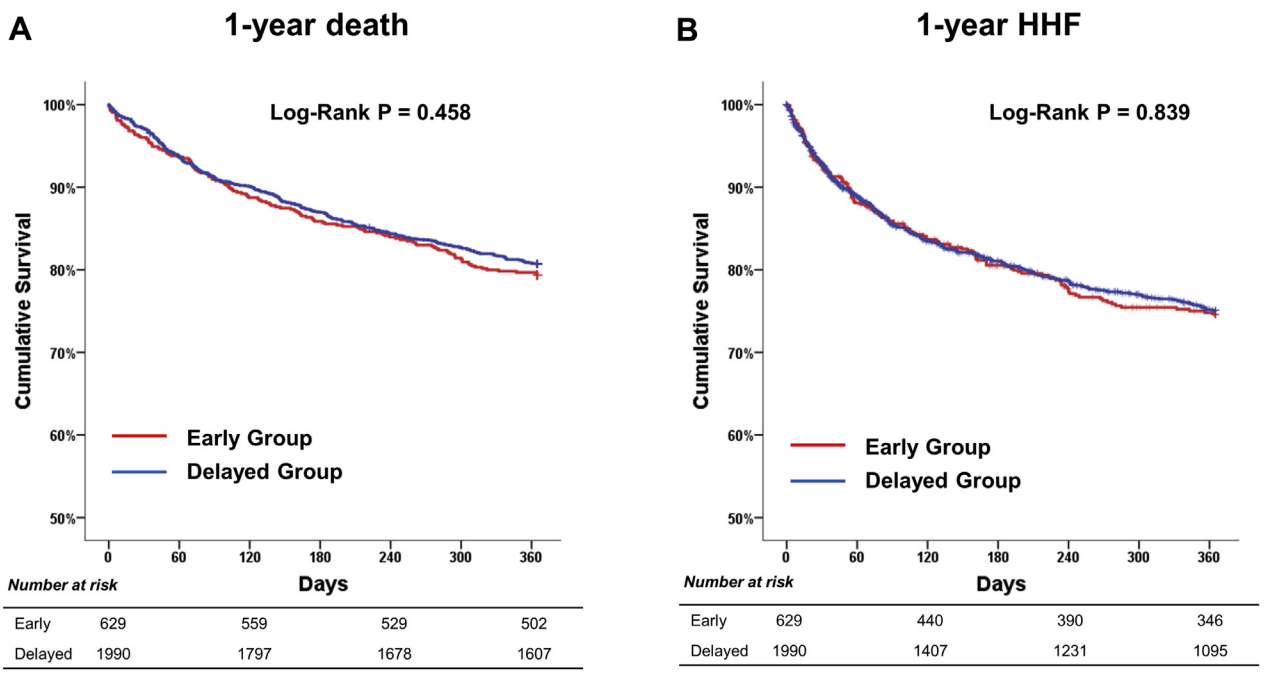
*Multivariable binary logistic regression adjusted for age, sex, ischemic heart disease, valvular heart disease, atrial fibrillation, COPD, current smoking, CRT, NYHA functional class, systolic blood pressure, heart rate, and LVEF. †Cox-proportional hazard regression analysis adjusted for age, sex, ischemic heart disease, valvular heart disease, atrial fibrillation, COPD, current smoking, CRT, NYHA functional class, systolic blood pressure, heart rate, LVEF, use of beta blockers, renin-angiotensin system inhibitors, and mineral corticoid receptor antagonists at discharge.

AC = all-cause; other abbreviations as in Tables 1 and 2.

AHF is a "subacute" process with a remote trigger, followed by successive hemodynamic and clinical congestion, which can be reversed with diuretic therapy. Currently there is no targeted therapy for the pathophysiology of AHF (13) and there is a relatively long time interval between the trigger and full-blown AHF. Therefore, the length of D2D time on clinical outcomes in patients with AHF has a limited role compared with door-to-balloon time in patients with STEMI.

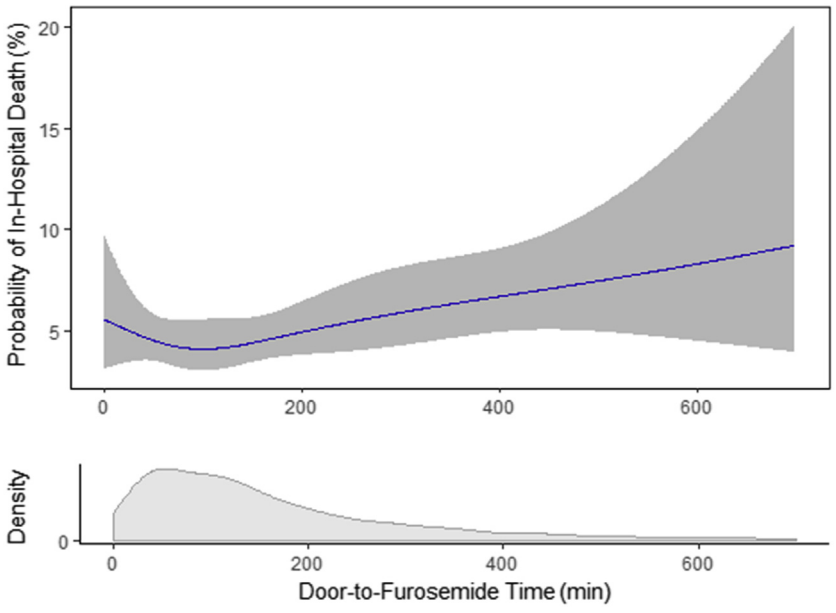
In the RELAX-AHF (Relaxin in Acute Heart Failure) trial (14), treatment with serelaxin was associated with substantial improvement of dyspnea and biomarkers of organ injury and reduced 180-day mortality rates, thereby supporting the hypothesis that myocardial damage is a progressive phenomenon in patients with AHF, and early treatment mitigating this organ damage could improve outcomes. In contrast, larger studies designed to evaluate the effect of early administration of nesiritide in the ASCEND-HF (the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure) trial (15) and ularitide in the TRUE-AHF (Trial of Ularitide's Efficacy and Safety in patients

FIGURE 3 Post-Discharge 1-Year Outcomes



Rates of **(A)** 1-year post-discharge death and **(B)** 1-year rehospitalization did not differ between the groups. HHF = hospitalization for heart failure.

FIGURE 4 Probability Plot for In-Hospital Mortality



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

with Acute Heart Failure) trial (16) failed to show survival benefit despite rapid improvement of congestion.

STUDY LIMITATIONS. First, this was not a randomized controlled study that was specifically designed to evaluate the impact of D2D time on clinical outcomes in patients with AHF. Therefore, the possibility that confounding factors may have influenced the study results cannot be ruled out, although we performed several sensitivity analyses including multivariable adjustment and propensity score matching. Nevertheless, the large sample size with sufficient power makes the neutral association between D2D time and clinical outcomes less prone to type I error. Indeed, our study is a large *prospective* cohort study that investigated the effect of D2D time on in-hospital and post-discharge outcomes. Second, the timing and dose of initial intravenous furosemide were not uniform, and the diuretic effect was not monitored. Third, because we included only East Asians who had different patients' characteristics compared with representative AHF cohorts from the United States (17) and Europe (18), the study results cannot be generalized to all patients with HF. Most importantly, given the nature of the study design, the study results are at best hypothesis generating, and the effect of D2D time on clinical outcomes must be confirmed in successive confirmatory studies.

CONCLUSIONS

D2D time was not associated with clinical outcomes in this large cohort of patients with AHF.

ADDRESS FOR CORRESPONDENCE: Dr. Dong-Ju Choi, Cardiovascular Center, Seoul National University Bundang Hospital, College of Medicine, Seoul National University, Gumiro 166, Bundang, Seongnam, Gyeonggi-do, Republic of Korea. E-mail: djchoi@snubh.org.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with AHF who were presenting to an ED, D2D time was not associated with either in-hospital or post-discharge outcomes.

TRANSLATIONAL OUTLOOK: Given the observational nature of this study, the definitive effect of D2D time on mortality should be investigated in successive clinical studies.

REFERENCES

1. Ponikowski P, Voors AA, Anker SD, et al. [2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure]. Kardiol Pol 2016;74:1037–47.

2. Mebazaa A, Yilmaz MB, Levy P, et al. Recommendations on pre-hospital & early hospital management of acute heart failure: a consensus paper from the Heart Failure Association of the European Society of Cardiology, the European Society of Emergency Medicine and the Society of Academic Emergency Medicine. Eur J Heart Fail 2015;17:544–58.

3. McNamara RL, Wang Y, Herrin J, et al. Effect of door-to-balloon time on mortality in patients with ST-segment elevation myocardial infarction. J Am Coll Cardiol 2006;47:2180–6.

4. Cannon CP, Gibson CM, Lambrew CT, et al. Relationship of symptom-onset-to-balloon time and door-to-balloon time with mortality in patients undergoing angioplasty for acute myocardial infarction. JAMA 2000;283:2941–7.

5. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61:e78–140.

6. Matsue Y, Damman K, Voors AA, et al. Time-to-furosemide treatment and mortality in patients hospitalized with acute heart failure. J Am Coll Cardiol 2017;69:3042–51.

7. Lee SE, Cho HJ, Lee HY, et al. A multicentre cohort study of acute heart failure syndromes in Korea: rationale, design, and interim observations of the Korean Acute Heart Failure (KorAHF) registry. Eur J Heart Fail 2014;16:700–8.

8. Lee SE, Lee HY, Cho HJ, et al. Clinical characteristics and outcome of acute heart failure in Korea: results from the Korean Acute Heart Failure Registry (KorAHF). Korean Circ J 2017;47:341–53.

9. Peterson PN, Rumsfeld JS, Liang L, et al. A validated risk score for in-hospital mortality in patients with heart failure from the American Heart Association Get With the Guidelines Program. Circ Cardiovasc Qual Outcomes 2010;3:25–32.

10. Gibson CM. Time is myocardium and time is outcomes. Circulation 2001;104:2632–4.

11. Adamson PB, Magalski A, Braunschweig F, et al. Ongoing right ventricular hemodynamics in heart failure: clinical value of measurements derived from an implantable monitoring system. J Am Coll Cardiol 2003;41:565–71.

12. Abraham WT, Adamson PB, Bourge RC, et al. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. Lancet 2011;377:658–66.

13. Januzzi JL Jr., Felker GM. Door-to-furosemide therapy in the ED: new quality metric or just a piece of the puzzle? J Am Coll Cardiol 2017;69:3052–4.

14. Teerlink JR, Cotter G, Davison BA, et al. Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial. Lancet 2013;381:29–39.

15. O'Connor CM, Starling RC, Hernandez AF, et al. Effect of nesiritide in patients with acute decompensated heart failure. N Engl J Med 2011;365:32–43.

16. Packer M, O'Connor C, McMurray JJV, et al. Effect of ularitide on cardiovascular mortality in acute heart failure. N Engl J Med 2017;376:1956–64.

17. Fonarow GC, Heywood JT, Heidenreich PA, et al. Temporal trends in clinical characteristics, treatments, and outcomes for heart failure hospitalizations, 2002 to 2004: findings from Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J 2007;153:1021–8.

18. Nieminen MS, Brutsaert D, Dickstein K, et al. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. Eur Heart J 2006;27:2725–36.

KEY WORDS acute heart failure, door-to-diuretic time, outcomes

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