Clinical Investigation

Very Early Diuretic Response After Admission for Acute Heart Failure

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ABSTRACT

Background: In hospitalized heart failure patients, a poor diuretic response (DR) during the first days of hospital admission is associated with worse outcomes. However, it remains unknown whether DR in the first hours has similar prognostic value. Moreover, data on the sequential change in DR during hospital admission are lacking.

Methods and Results: DR (urine output per 40-mg furosemide-equivalent diuretics dose) was measured from 0 to 6 hours (DR6), 6 to 48 hours (DR6-48), and 0 to 48 hours (DR48) of the patient's emergency department (ED) arrival in 1551 patients with acute heart failure (AHF; mean age 78 years, 56% male, and 48% de novo patients with heart failure). Patients with a poor DR within the first 6 hours were older age, had worse renal function, and were already on diuretic treatment before admission. DR6 was only weakly correlated with DR6-48 (Spearman's rho = 0.273; $P < .001$). DR6, DR6-48, and DR48 were all significantly associated with 60-day mortality independent of other prognostic factors. DR6 and DR48 showed comparable prognostic ability. However, the model combining DR6 with DR6-48 significantly exceeded both DR6 (net reclassification improvement 0.249; $P = .032$) and DR48 (net reclassification improvement 0.287; $P = 0.025$) with regard to 60-day mortality prediction.

Conclusions: DR measured within the first 6 hours of ED arrival and DR measured during the first 48 hours in patients with AHF have similar prognostic value, although they were moderately correlated. Changes in DR over time provide additional prognostic information. (*J Cardiac Fail 2019;25:12−19*)

Keywords: Diuretic resistance, risk stratification, prognosis.

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Introduction

Intravenous loop diuretics are the cornerstone of treatment of hospitalized heart failure patients.[1−3] A poorer response to diuretic treatment was consistently related to worse outcomes. Poor renal function, low systolic blood pressure, ischemic etiology of heart failure, and diabetes are associated with poor diuretic response (DR) 24−96 hours after hospital admission.[4−6] Therefore, strategies to improve DR in hospitalized heart failure patients are currently being considered. However, some important information for these strategies is currently missing. Most importantly, it is yet unknown how long we should measure DR to use it for risk stratification. In previous studies, the period of DR evaluation widely ranged from 24 hours to up to 4 days according to the definitions used in each study. If DR in the first hours has the same prognostic value as DR 24−96 hours after hospital admission, patients with a poor DR can be identified at an earlier stage and therefore treated earlier and more efficiently. However, the clinical significance of DR measured for periods <24 hours has not been elucidated.

Another point that remains unknown is clinical importance of temporal changes in DR. All previous studies evaluated DR for only 1 time period, and DR has always been assumed to be constant during the measurement period. However, no study has investigated the changes in DR over time and its prognostic implications.

REALITY-AHF (Registry Focused on Very Early Presentation and Treatment in Emergency Department of Acute Heart Failure) was a prospective multicenter registry focusing on the association between acute phase treatment and prognosis of patients who had a heart failure hospital admission. Enrollment was performed from August 2014 to December 2015. Among the 20 participating hospitals, 9 were university hospitals and 11 were nonuniversity teaching hospitals. The primary objective of this registry was to investigate the prognostic impact of timing of treatment. Therefore, the amount of diuretics used and urine output were repetitively evaluated during the first 48 hours after the patient's ED arrival. This study design enabled us to evaluate and compare DR evaluated in different time periods in terms of prognostic predict ability. In the current secondary analysis of REALITY-AHF, we aimed to (1) evaluate if DR within 6 hours predicted prognosis as efficiently as DR within 48 hours and (2) test if serial changes in DR over time provided additional prognostic information in patients with acute heart failure (AHF).

Methods

Study Design and Patients

This was a retrospective post hoc analysis of REALITY-AHF, in which 1682 consecutive patients with hospitalized AHF were prospectively registered. Enrollment was performed from August 2014 to December 2015. Among the 20 participating hospitals, 9 were university hospitals and 11 were nonuniversity teaching hospitals. The study design and primary outcomes have been described elsewhere.[7] Briefly, we enrolled patients aged ≥20 years diagnosed with AHF in the emergency department (ED) within 3 hours from the first evaluation by caregivers and hospitalized through the ED. The exclusion criteria were (1) treatment with an intravenous drug started prior to ED arrival, (2) history of heart transplantation, (3) patient on chronic peritoneal dialysis or hemodialysis, (4) acute myocarditis, and (5) acute coronary syndrome requiring emergency revascularization. Patients with a brain natriuretic peptide (BNP) level < 100 pg/mL or N-terminal-proBNP level < 300 pg/mL at baseline and patients with missing BNP and N-terminal-proBNP data were also excluded. All patients were enrolled at the ED, and baseline data including physical findings, echocardiography, and laboratory data were collected at the ED.

We used prognostic endpoints of 60-day all-cause mortality. All patients were followed up for 1 year after discharge, and prognostic information was prospectively collected. For those without follow-up data in the clinics where the patient was registered, prognostic data was obtained from telephone interviews with the medical records department of other medical facilities that managed the patient or with the family.

REALITY-AHF complies with the Declaration of Helsinki and Japanese Ethical Guideline for Medical and Health Research Involving Human Subjects. 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. The study protocol was approved by the ethics committee of each participating hospital. Study information including the objectives, inclusion and exclusion criteria, and the names of participating hospitals were published in the publically available University Hospital Information Network (UMIN-CTR, unique identifier: UMIN000014105) before the first patient was enrolled.

Diuretic Response

DR was defined as urine output (in milliliters) obtained per 40 mg of intravenous furosemide (or equivalent). Oral furosemide was converted to half the dose of intravenous furosemide. The doses of oral loop diuretics that were considered equivalent to 40 mg of intravenous furosemide were 10-mg torsemide and 60-mg azosemide. In REALITY-AHF, data on urine output was prospectively collected in predefined time windows of 0−1.5, 1.5−6, 6−24, and 24−48 hours. However, data on the amount of intravenous and oral diuretics used were available only for the time windows of 0−6 and 0−48 hours. Therefore, we defined DR based on the urine output for 3 time windows: 0−6 hours (DR6), 6−48 hours (DR6-48), and 0−48 hours (DR48).

Statistical Analysis

Data are expressed as mean and standard deviation for normally distributed variables, and as median with interquartile range (IQR) for non-normally distributed data. Categorical data are expressed as numbers and percentages. The relationship between baseline characteristics and tertile groups of each DR6, DR6-48, and DR48 was examined

using the 1-way analysis of variance, Kruskal-Wallis, or chi-square tests, where appropriate. The Cochran-Armitage trend test was used to test for a trend. When necessary, variables were transformed for further analyses. Correlations between DRs were evaluated using Spearman's rho.

In multivariable linear regression analyses, we constructed 4 models: (1) DR6 as the outcome including baseline (hour 0) variables as predictors to see which variables measurable at baseline can predict DR6; (2) DR6-48 as the outcome including baseline (hour 0) variables as predictors to see which variables measurable at baseline can predict DR 6-48; (3) DR6-48 as the outcome including DR6, heart rate, and systolic and diastolic blood pressure at 6 hours instead of these parameters measured at baseline (hour 0) to see how much of DR6-48 can be predicted by DR6 and other data available at 6 hours after ED arrival; and (4) DR48 as the outcome including baseline (hour 0) variables as predictors to see how much we can predict DR48 at the time of starting treatment. Multivariable linear regression analysis was performed using backward elimination method after including all variables with a P value <.10 in univariate analysis. For prognostic analysis, we selected the following variables as preexisting and known prognostic factors: age, history of heart failure, New York Heart Association functional class, systolic blood pressure, hemoglobin, serum sodium, blood urea nitrogen, and BNP at admission. These variables were used for adjustment in a multivariable Cox regression model. To account for missing covariate data, multiple imputation was used. We created 20 datasets using a chained-equations procedure.[8,9] Parameter estimates were obtained for each dataset and subsequently combined to produce an integrated result using the method described by Barnard and Rubin.[10]

To evaluate the additive prognostic value of scores, we constructed the following 3 models for 60-day all-cause mortality: a DR6 model constructed using DR6 alone; a DR6 + DR6-48 model constructed incorporating DR6 and DR6-48, and a DR48 model that used DR48 alone. Receiver operating characteristics curves and their areas under the curve (AUCs) were evaluated. Confidence intervals for the AUCs were obtained with 2000-bootstrap resampling. AUCs were compared using the Wald test based on the empirical standard deviation performing 2000-times resampling.[11] We also calculated the continuous (as opposed to the categorical) net reclassification improvement (NRI) with its corresponding 95% confidence interval to evaluate the incremental predictive ability.[12]

Statistical analyses were performed using R version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org). A 2-sided P value <.05 was considered statistically significant.

Results

Patient Baseline Characteristics for DR

The study flowchart is shown in Fig. 1. The REALITY-AHF cohort comprised 1682 patients with AHF after excluding 80 of 1762 registered patients. Furthermore, we excluded another 22 patients who were discharged within 2 days, 88 patients who were neither treated with intravenous nor oral loop diuretics, and 21 patients whose data on diuretics use were missing; thus, 1551 patients remained. The mean age was 78 years, 56% were male, and 48% were de novo patients with heart failure. After excluding patients without data on either urine output or diuretic use, data on DR6, DR6-48, and DR48 were available in 1071, 976, and 1471 patients, respectively. We also excluded patients with extremely high (>99th percentile) or low (<1st percentile) values for each DR (n = 22 for DR6, n = 20 for DR6-48, and n = 29 for DR48) owing to the unreliability of such values, and 1049, 956, and 1452 patients, respectively, were included in the final analysis.

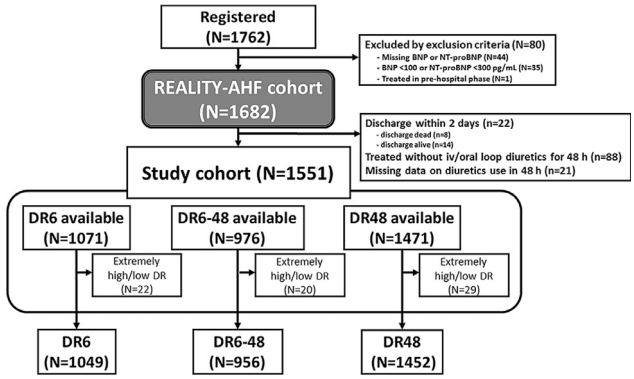

Fig. 1. Study flowchart.

Baseline characteristics according to tertile groups in DR6, DR6-48, and DR48 are described in Table 1 and Supplemental Table 1. Overall, poor DR was associated with older age; low blood pressure and heart rate; history of heart failure; and being treated with heart failure medications including diuretics, beta-blockers, and aldosterone blockers. Regarding biomarkers, high white blood cell count, low serum albumin, low hemoglobin, low aspartate aminotransferase, high creatinine and blood urea nitrogen, high potassium, high glucose, high C-reactive protein, and high BNP levels were associated with poor DR.

The results of univariate linear regression (Supplemental Table 2) and multivariable linear regression for each DR showed that older age and higher serum creatinine and diuretic prescriptions at baseline were associated with poor DR in all 3 time periods (Table 2). In the model using DR6 and data at 6 hours, DR6 was the most powerful predictor of DR6-48; however, the final model consisting of all independent predictors including DR6 explained only 8.8% of DR6-48. Supplemental Figure 1 shows the correlation of DR6 vs DR48 and DR6 vs DR6-48. DR6 was significantly but weakly correlated with DR6-48 (Spearman's rho = 0.273; P < .001) and moderately correlated with DR48 (Spearman's rho = 0.544; P < .001).

Prognostic Values of DR6, DR48, and DR6 + DR6-48

The overall 60-day follow-up rate was 97.4%, and 120 patients died during each follow-up period. Mortality rate

Table 1. Baseline Characteristics of Patients According to DR6

Variables	DR6			*P* value
	T1 (poor; n = 356)	T2 (n = 357)	T3 (n = 336)	
Age, y	80 ± 11	78 ± 11	76 ± 14	<.001
Male gender (%)	196 (55.1)	193 (54.1)	186 (55.4)	.937
Arrived by ambulance (%)	226 (63.5)	223 (62.5)	173 (51.5)	.002
Systolic blood pressure, mm Hg	151 ± 37	152 ± 37	155 ± 31	.179
Diastolic blood pressure, mm Hg	82 ± 24	86 ± 27	89 ± 24	.002
Heart rate, beats/min	99 ± 28	98 ± 28	101 ± 29	.361
NYHA III or IV (%)	307 (89.5)	290 (83.3)	283 (87.1)	.056
Symptom onset time (%)				.340
≤6 h	85 (23.9)	85 (23.8)	80 (23.8)	
6 h to 2 d	94 (26.4)	76 (21.3)	69 (20.5)	
>2 d	177 (49.7)	196 (54.9)	187 (55.7)	
ECG rhythm (%)				.703
Sinus	204 (57.5)	197 (55.2)	182 (54.3)	
AF	126 (35.5)	129 (36.1)	131 (39.1)	
Others	25 (7.0)	31 (8.7)	22 (6.6)	
LVEF at ED (%)				.469
<35%	117 (35.7)	123 (36.6)	111 (35.9)	
35−50%	113 (34.5)	96 (28.6)	92 (29.8)	
>50%	98 (29.9)	117 (34.8)	106 (34.3)	
Physical examination (%)				
JVD	219 (62.8)	226 (63.7)	214 (64.5)	.898
Orthopnea	254 (71.8)	227 (63.6)	216 (64.3)	.039
Rale	259 (73.0)	256 (71.7)	232 (69.3)	.551
Peripheral edema	251 (70.7)	259 (72.5)	256 (76.2)	.256
Pulmonary edema	281 (78.9)	265 (74.2)	260 (77.4)	.317
Comorbidities (%)				
History of heart failure	193 (54.2)	193 (54.1)	140 (41.7)	.001
Hypertension	254 (71.3)	233 (65.3)	241 (71.7)	.113
Diabetes mellitus	130 (36.5)	144 (40.3)	109 (32.4)	.098
COPD	44 (12.4)	30 (8.4)	37 (11.0)	.218
Coronary artery disease	118 (33.1)	108 (30.3)	90 (26.8)	.190
Medication at admission (%)				
Loop diuretics	206 (57.9)	189 (53.1)	120 (36.3)	<.001
ACE-I	61 (17.2)	64 (17.9)	54 (16.1)	.809
ARB	110 (31.0)	118 (33.1)	105 (31.2)	.813
Beta-blocker	158 (44.8)	151 (42.5)	122 (36.4)	.072
Aldosterone blocker	67 (18.8)	88 (24.6)	57 (17.0)	.030
Laboratory data				
WBC, μL	8500 (6200,11400)	7400 (5800,9500)	7300 (5600, 9225)	<.001
Albumin, g/dL	3.4 ± 0.6	3.5 ± 0.5	3.6 ± 0.5	<.001
Hemoglobin, g/dL	11.4 ± 2.1	12.0 ± 2.3	12.1 ± 2.4	<.001
AST, IU/L	32 (23, 50)	30 (23, 45)	34 (25, 48)	.192
ALT, IU/L	20 (13, 35)	21 (14, 34.50)	25 (17, 39.25)	.002
Creatinine, mg/dL	1.3 (0.9, 2.0)	1.2(0.8, 1.5)	1.0 (0.8, 1.3)	<.001
BUN, mg/dL	30 (22, 44)	24 (17, 31)	21 (16, 28)	<.001
Sodium, mEq/L	139 (137, 142)	140 (137, 142)	140 (137, 142)	.081
Potassium, mEq/L	4.4 ± 0.8	4.4 ± 0.6	4.1 ± 0.6	<.001
Glucose, mg/dL	171 ± 78	174 ± 82	158 ± 73	.026
CRP, mg/dL	0.85 (0.30, 2.85)	0.59 (0.21,1.73)	0.43 (0.12, 1.46)	<.001
BNP, pg/mL	912 (494, 1641)	702 (436,1259)	671 (388, 1170)	<.001
Length of hospital stay, d	16 (10, 28)	16 (10, 25)	16 (11, 24)	.657
Type of diuretic administered				
Furosemide	355 (99)	356 (99)	334 (99)	0.131
Azosemide	5 (1)	11 (3)	4 (1.2)	0.742
Torsemide	1 (0.3)	3 (0.8)	3 (0.9)	0.542

ACE-I, angiotensin-converting enzyme inhibitor; ALT, aspartate aminotransferase; ARB, angiotensin II receptor blocker; AST, alanine aminotransferase; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; ECG, electrocardiogram; ED, emergency department; JVD, jugular venous distention; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; WBC, white blood cell count

for 60 days stratified by tertiles of DR6, DR6-48, and DR48 are shown in Fig. 2, and poorer DR was significantly associated with higher 60-day mortality in all DRs (*P* for trend <.01 for all DRs). In the univariate and multivariable Cox regression analysis, all DRs were associated with 60-day mortality even after adjustment for other prognostic factors when they were individually evaluated (Table 3). When both DR6 and DR6-48 were entered into the same Cox model, both were associated with 60-day mortality in univariate analysis, but only DR6 was significantly associated with 60-day mortality after adjustment for other covariates (Supplemental Table 3). Among 1551 patients, 172 (11%)

Table 2. Multivariate Linear Regression Analysis for DR6, DR6-48, and DR48

Variables	MV Linear Regression for DR6 (adjusted $R^2 = 0.140$)			Variables	MV Linear Regression for DR6-48(adjusted $R^2 = 0.065$)			Variables	MV Linear Regression for DR6-48 With DR6 (adjusted $R^2 = 0.088$)			Variables	MV Linear Regression for DR48 (adjusted $R^2 = 0.109$)		
	Standardized Beta	*t* Value	*P* Value		Standardized Beta	*t* Value	*P* Value		Standardized Beta	*t* Value	*P* Value		Standardized Beta	*t* Value	*P* Value
Creatinine	−0.152	−3.91	<.001	On diuretics at baseline	−0.171	−5.10	<.001	DR6	0.204	6.336	<.001	On diuretics at baseline	−0.199	−7.48	<.001
Age	−0.151	−4.18	<.001	CRP	−0.092	−2.83	.005	On diuretics at baseline	−0.164	−5.105	<.001	Age	−0.129	−4.67	<.001
On diuretics at baseline	−0.150	−4.13	<.001	Rale	−0.079	−2.40	.016	CRP	−0.098	6.336	<.001	Systolic blood pressure	0.836	3.18	.002
WBC	−0.142	−3.95	<.001	Creatinine	−0.078	−2.39	.017					ALT	0.079	3.049	.002
Potassium	−0.104	−2.80	.005	Systolic blood pressure	0.071	2.10	.036					Hemoglobin	−0.078	−2.713	.006
Albumin	0.090	2.47	.014	Age	−0.064	−1.98	.048					BUN	−0.077	−2.17	.029
BNP	−0.073	−2.00	.046									Creatinine	−0.075	−2.19	.029

MV, multivariable; other abbreviations as in Table 1.

were treated with tolvaptan and 627 (40.4%) were treated with carperitide within 48 hours. We checked the interaction between these drugs and the prognostic value of DR in the Cox model, and no significant interaction was found (Supplemental Table 4).

We grouped patients with available DR6 and DR6-48 into 9 groups according to the tertiles of DR6 and DR6-48, and more than half of patients in each tertile of DR6 were categorized into different tertiles of DR6-48. Unadjusted mortality tended to increase with decreasing DR6-48 in all tertile groups of DR6 (Fig. 3).

To evaluate the difference in prognostic predictive ability, we compared the AUCs of the DR6 model, DR6 + DR6-48 model, and DR48 model for 60-day mortality (Table 4). There was no statistically significant difference in AUC and NRI between DR6 and DR48 for 60-day mortality. However, when DR6-48 was added to DR6, we found a net 24.9% improvement compared with DR6 and a 28.7% improvement compared with DR48 in predicting 60-day mortality. We also compared DR6 and DR6-48 and did not observe a significant difference in prognostic predict ability (P = .768 for AUC comparison; NRI −0.005; P = .948).

Discussion

In this study, we addressed 2 questions regarding DR that have remained unanswered in patients with AHF. For the first question ("Does very early DR carry the same predictive value as DR during hospital admission?"), we compared DR6 and DR48. DR measured within the first 6 hours of the patient's ED arrival was significantly associated with 60-day mortality and performed comparable to DR measured within 48 hours. For the second question ("Does DR change over time, and what is its prognostic implication?"), we compared DR6 and DR6-48. Both entities showed only a notably weak association, and DR6 poorly predicted DR6-48. Taken together with our finding that DR6-48 provides additive prognostic information on top of DR6, this suggests that patients with a poor DR in the first 6 hours are not necessarily the same patients as those with a poor DR from 6 to 48 hours, although both groups have poorer outcomes.

Prognostic Information of DR Within 6 Hours

The similar prognostic information of DR6 and DR48 is clinically and scientifically relevant because it enables an earlier identification of patients at high risk in the acute setting. DR was initially introduced as an objective method to evaluate diuretic resistance, which was defined as body weight changes in 4 days per 40 mg of furosemide-equivalent diuretics.[5,13] Although subsequent studies have consistently shown that poor DR is strongly and independently associated with a poor prognosis, very few studies compared the prognostic values between DR measured in different time periods. In the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) dataset, DR based on weight

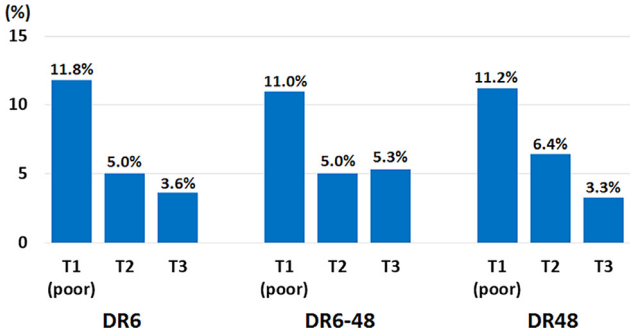

Fig. 2. Sixty-day mortality according to the tertiles of DR6, DR6-48, and DR48. DR, diuretic response.

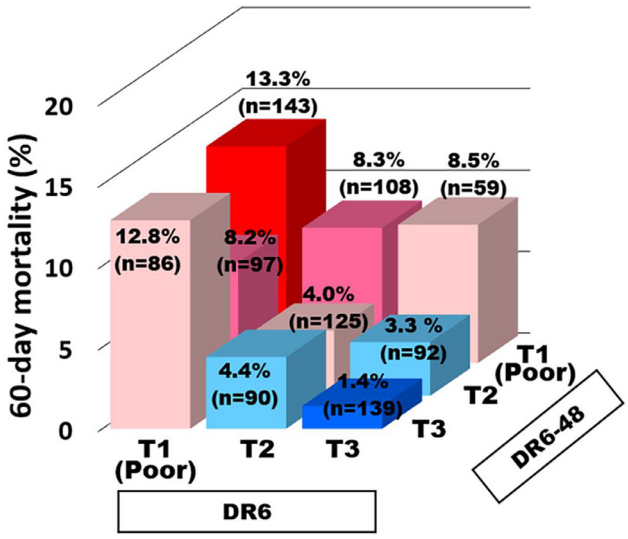

Fig. 3. Sixty-day mortality, tertiles of DR6, and tertiles of DR6-48. These plots shows the relationship of 60- and 180-day mortality to the tertiles of DR6 and DR6-48. DR, diuretic response.

change in the first 48 hours of admission and DR with urine output within 24 hours were evaluated.[6] The 2 DRs were modestly correlated with each other, and both were associated with a combined endpoint of death and heart failure rehospitalization independent of other covariates. These findings are in line with ours in the sense that DR evaluated in a shorter period does not imply a less capable prognostication. Moreover, the study found that only DR based on urine output, but not DR in 24 hours based on body weight, was an independent predictor of 180-day mortality.

It is yet unclear whether changes in body weight, net fluid output, or urine output should be used for measurement of DR in terms of better risk stratification, and there are some drawbacks in using urine output to determine DR compared with body weight.[14] Nevertheless, our study results may highlight the potential utility of very early DR based on urine output. Moreover, it may be difficult to weigh some patients before their condition is stabilized. This study, for the first time, showed the utility of short-term DR measurement in the ED setting in terms of risk stratification. Although the prognostic capability of DR based on urine or body weight in 6 hours or even within a shorter time period is yet to be determined, our study results expand the clinical utility of DR to the ED phase in which very prompt risk stratification of the AHF patient is required. Finally, our findings may contribute to better clinical study designs through a more accurate and prompt identification of high-risk AHF patients. This is also important because recent studies have highlighted the importance of early treatment in AHF patients.[7,15,16]

Variability in DR

Considering that we could capture all patients from the beginning of treatment (ie, ED arrival), unlike in previous studies, it was possible to ascertain acute DR and its variability with time in AHF. Our study results suggest that considerable interpatient DR fluctuation occurs over time because less than half of the patients remained in the same tertile of DR in the 2 time periods, and DR6 and DR6-48 were weakly associated (Spearman's rho = 0.275: $P < .001$). In addition, we found that it was difficult to predict DR6-48 even if DR6 was taken into consideration. These findings imply that the fluctuation of DR over time is not rare, and this fluctuation is not easily predictable. In contrast, findings from the Placebo-Controlled Randomized Study of the Selective A(1) Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized With Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect

Table 3. Univariate and Multivariable Cox Regression Analysis for 60- and 180-Day Mortality

Variables	60-Day Mortality					
	Univariate Cox Model			Multivariable Cox Model (full adjustment*)		
	Hazard Ratio	95% CI	*P* Value	Hazard Ratio	95% CI	*P* Value
DR in 6 h						
DR in 6 h (per 100 mL increase)	0.96	0.94–0.98	.002	0.95	0.95–0.99	.021
DR in 6–48 h						
DR in 6–48 h (per 100 mL increase)	0.99	0.98–0.99	.003	0.99	0.98–0.99	.045
DR in 48 h						
DR in 48 h (per 100 mL increase)	0.97	0.96–0.99	<.001	0.98	0.97–0.99	.002

CI, confidence interval; DR, diuretic response.

*Adjusted for age, gender, New York Heart Association functional class, systolic blood pressure, heart rate, history of heart failure, history of diabetes, left ventricular ejection fraction, prescription of beta-blocker, prescription of angiotensin inhibitor or angiotensin II receptor blocker at admission, hemoglobin, serum sodium, serum creatinine, blood urea nitrogen, brain natriuretic peptide, and C-reactive protein.

Table 4. Comparison of AUCs of the DR6, DR48, and DR6 + DR6-48 Models for 60-Day Mortality and NRI

		Updated Model for 60-Day Mortality	
		DR48 Model (AUC 0.66, 95% CI 0.61−0.72)	DR6 + DR6-48 Model (AUC 0.68, 95% CI 0.61−0.74)
Baseline Model for 60-Day Mortality	DR6 model (AUC 0.67, 95% CI 0.60−0.73)	AUC diff −0.006, $P = .828$	AUC diff +0.03, $P = .697$
		NRI 0.030, 95% CI −0.218 to 0.277, $P = .815$	NRI 0.249, 95% CI 0.021−0.477, $P = .032$
	DR48 model (AUC 0.66, 95% CI 0.61−0.72)		AUC diff +0.03, $P = .596$
			NRI 0.287, 95% CI 0.035−0.538, $P = .025$

AUCs, areas under the curve; diff, difference; NRI, net reclassification improvement.

on Congestion and Renal Function (PROTECT) showed that DR based on weight change in 24 hours and on day 4 were well correlated.[17] This might be attributable to the difference in the definition of DRs, in the sense that body weight might not be as volatile as urine volume for reflecting sequential changes in DR. It could also be hypothesized that diuresis most often occurred within 24 hours. Indeed, our results showed that only DR6 was associated with mortality when the 2 metrics were put together in the same multivariate Cox model. At the same time, however, taking both metrics into account was shown to contribute to better prognostic prediction, which implies the value of measuring serial changes in DR within 48 hours. Given that DR has been, by definition, configured with the assumption that diuretics yield urine output constantly during the measurement period, our finding is both scientifically and clinically relevant because it shows that DR is not constant but variable and that the fluctuation of DR is prognostic. The main driver of the DR fluctuation has yet to be elucidated. It could be the change in responsiveness to diuretic therapy itself. However, it could also be the action subsequently taken by the physician in response to early DR.

Study Limitations

In this retrospective post hoc analysis, several study limitations need to be acknowledged. Our study cohort was almost all Japanese, and generalizability of our results is not clear. Moreover, almost half of all patients were those without history of heart failure and taking no heart failure drug at the time of admission. Although we checked the impact of history of heart failure on the association between DR and prognosis, and found no significant interaction (data not shown), this point should be taken into account for the interpretation of our study results. The protocol of the diuretic therapy was at the discretion of the physicians. Some patients were treated with drugs (eg, tolvaptan and carperitide) that might have affected the association between DR and prognosis. This point should also be taken into account as a potential bias for our study results even though our interaction analysis results were not statistically significant. We did not have data on DR6 for all patients with DR48 data, because not all patients with DR48 data were treated with furosemide within 6 hours. This might have resulted in selection bias and the limited applicability of early DR. By design, this registry enrolled only patients hospitalized through the ED, and the generalizability of our study results to other AHF populations hospitalized through non-ED pathways is not clear. Moreover, the generalizability of our study results to AHF patients who are not hospitalized and are directly discharged from the ED should be interpreted carefully. We arbitrarily compared DR measured in 2 time periods (ie, 6 and 48 hours); however, it is still unclear when and how frequently DR should be measured to optimize its prognostic value. Testani et al.[18] showed that an equation using serum and urine creatinine concentration measured with a spot urine sample obtained 1 hour after diuretic use can accurately predict urine output. Thus, the applicability of this study result to even early DR prediction is well justified. However, only bumetanide was used in the study because of the wide variation in furosemide bioavailability. Given that a larger number of AHF patients are treated with furosemide instead of bumetanide, the applicability of the equation in patients treated with furosemide should be confirmed. Moreover, the study did not test the equation in the AHF cohort, and its prognostic value is unclear. Considering that the early identification of high-risk patients is more crucial in AHF than in the chronic heart failure population, DR with urine output or body weight, which has been clearly shown to be a prognostic predictor in several AHF cohorts, might be a more clinically applicable and reliable risk-stratification tool. Finally, accurate measure of urine output in the ED setting is not impossible but remains challenging, and the feasibility of this strategy should be tested in future studies.

Conclusions

DR measured during the first 6 hours of ED arrival based on urine output can predict prognosis as efficiently as DR measured during the first 48 hours in patients with AHF. DR can change over time, and accounting for this change contributes to a better prognostic prediction. Our study results underscore the utility of early DR and repetitive DR evaluation in patients with AHF.

Disclosures

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Supplementary Data

Supplementary data related to this article can be found at doi:10.1016/j.cardfail.2018.09.004.

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