Prognostic Value of BNP Reduction During Hospitalization in Patients With Acute Heart Failure

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ABSTRACT

Background: Prognostication of patients discharged after acute heart failure (AHF) hospitalization remains challenging. Body weight (BW) reduction is often used as a surrogate marker of decongestion despite the paucity of evidence. We thought to test the hypothesis that B-type natriuretic peptide (BNP) reduction during hospitalization has independent prognostic value in AHF.

Methods and Results: We studied the prognostic predictability of percentage BNP reduction achieved during hospitalization in patients from the REALITY-AHF study. Percentage BNP reduction was defined as (BNP on admission − BNP at discharge) / BNP on admission × 100. The primary endpoint was 1-year all-cause death. In 1028 patients (age, 77 ± 13 years; 57% male; left ventricular ejection fraction, 47 ± 16%) with AHF, median BNP level at admission was 747 ng/L (interquartile range, 439−1367 ng/L) and median percentage BNP reduction was 62.5% (interquartile range, 36.5−78.5%). The smallest percentage BNP reduction quartile had more than 2-fold higher risk of all-cause death than the greatest quartile (23.0% vs 9.7%, $P < .001$). After adjusting for covariates including BNP at discharge, the percentage BNP reduction was significantly associated with all-cause death (hazard ratio 0.96, 95% confidence interval 0.93−0.99, $P = .032$), whereas percentage BW reduction was not. Percentage BNP reduction was more predictive in patients with heart failure with reduced ejection fraction than in those with preserved ejection fraction.

Conclusions: The prognostic value of percentage BNP reduction during hospitalization was superior to that of percentage BW reduction and was independent of other risk markers, including BNP at discharge. (*J Cardiac Fail 2019;25:712−721*)

Key Words: Acute heart failure, B-type natriuretic peptide, prognosis.

Acute heart failure (AHF) is one of the most common causes of hospitalization in developed countries.[1] Although the prognosis of chronic HF has dramatically improved in the past decades, the morbidity and mortality of AHF remain high and approximately one-half of patients hospitalized for AHF are rehospitalized within 6 months with

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similar symptoms.[2,3] Congestion is the main cause of hospitalization for worsening HF and inadequate decongestion or incomplete diuresis therapy during hospitalization is associated with higher readmission rate.[4−6] Although guidelines recommend monitoring net urine output and body weight (BW), the data evaluating the relationship between the change in these markers of decongestion and clinical outcomes are sparse and the results have been inconsistent.[5,7−9]

B-type natriuretic peptide (BNP) has been established as one of the best prognostic makers in patients with HF.[10−12] As changes in BNP level reflect hemodynamic deterioration/improvement,[13,14] BNP reduction during hospitalization has the potential to add prognostic information that could help physicians' decision-making. However, clinical trials have shown inconsistent results on the prognostic utility of BNP,[15] and the importance of BNP reduction during hospitalization remains controversial.[16,17] The objective of the present study was to test the hypothesis that percentage BNP reduction during hospitalization has a prognostic value independent of pre-existing risk markers in patients with AHF including BNP level at discharge.

Methods

The present study was based on REALITY-AHF (Registry Focused on Very Early Presentation and Treatment in Emergency Department of Acute Heart Failure), which was a prospective multicenter registry focusing on presentation and treatment in very early phase of AHF hospitalization. In this registry, patients' data, including BW and natriuretic peptide level, were routinely collected both on admission and at hospital discharge. The detailed study design has been published elsewhere.[18,19] Briefly, the study was conducted in 20 hospitals in Japan and consecutive patients with AHF aged ≥20 years old who were hospitalized via the emergency department were enrolled. AHF was diagnosed by an attending physician at each site based on Framingham criteria.[20] Additionally, patients with BNP <100 ng/L or NTproBNP <300 ng/L were excluded because of uncertainty of the diagnosis as recommended by the guidelines.[21] Detailed inclusion/exclusion criteria and other study information were published in the publicly available University Hospital Information Network (UMIN-CTR, unique identifier: UMIN000014105) before the first patient was enrolled. Written informed consent was not required because of the observational nature of the study and we used an opt-out method for participant recruitment. The study protocol was in compliance with the Declaration of Helsinki and was approved by the local institutional review board of each hospital.

Percentage BNP Reduction and percentage BW Reduction

We evaluated the BNP level on admission at the emergency department and just before discharge after patients became stable; after the chief symptoms disappeared and all intravenous therapy finished. Patients with missing BNP level on admission or at discharge were excluded from the present analysis. Percentage BNP reduction was defined by the following formula: (BNP on admission − BNP at discharge) / BNP on admission × 100 (%). Patients were split into quartile groups based on percentage BNP reduction and their characteristics and outcomes were compared. BW was also measured on admission and just before discharge. Percentage BW reduction was defined as (BW on admission − BW at discharge) / BW on admission × 100 (%). Diuretic response in the first 6 hours was calculated on the basis of the urine output for a 40-mg furosemide-equivalent loop diuretic dose as previously described.[22]

Outcomes

The primary endpoint was predefined as all-cause death within 1 year of discharge. The composite endpoint of all-cause death and HF rehospitalization was also tracked. All patients were prospectively followed-up at least every 3 months after discharge up to 1 year. Additionally, patients were followed-up as clinically indicated. For those without follow-up in clinics, prognostic data were obtained from electric medical chart and telephone interviews. HF rehospitalization was predefined as HF readmission only if the criteria for HF readmission described in the American College of Cardiology/American Heart Association Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials were fulfilled.[19,23]

Statistical Analysis

Data are presented as mean ± SD or median [1st−3rd quartile] for continuous variables and as frequency (%) for categorical variables. One-way ANOVA or the Kruskal−Wallis test were used to compare continuous variables. The χ^2 test or Fisher's exact test was used to compare categorical variables. The correlation between percentage BNP reduction and percentage BW reduction was assessed with Spearman's correlation test. The log rank test and Kaplan−Meier curve analysis were used to compare the event-free rate among the percentage BNP reduction quartiles. To compare the association with the events, receiver-operator-characteristic (ROC) curve analysis was performed and area under the curve (AUC) were compared using DeLong's method.[24] To identify the independent impact of percentage BNP reduction on the outcomes, multivariate Cox regression models were constructed with adjustment for well-established risk markers evaluated at the time of discharge (age, sex, past history of HF, diabetes mellitus, ischemic etiology, prescription of angiotensin-converting-enzyme inhibitor or angiotensin II receptor blocker, prescription of beta blocker, New York Heart Association [NYHA] class, systolic blood pressure, hemoglobin level, blood urea nitrogen level, serum sodium level, estimated glomerular filtration rate, and BNP level). As a sensitivity analysis, we also constructed Cox regression models using MAGGIC (the Meta-analysis Global Group in Chronic Heart Failure) score and BNP level at discharge

as adjustment variables, because MAGGIC score is a well-validated risk score for Japanese patients with HF.[25−27] Continuous net reclassification improvement (NRI) was calculated to evaluate the incremental value of BNP reduction from the baseline models.[28] To clarify whether obtained results were consistent even if we took missing data (mainly on BNP levels) into account, multiple imputation was used. We created 20 datasets using a chained-equations procedure.[29,30] Parameter estimates were obtained for each dataset and subsequently combined to produce an integrated result using the method described by Barnard and Rubin.[31] All statistical analyses were performed with R (The R Foundation for Statistical Computing, Vienna, Austria) and its graphical user interface, EZR (version 2.41; Saitama Medical Center, Jichi Medical University, Saitama, Japan).[32] In all analyses, a two-tailed *P*value <.05 was considered statistical significance.

Results

Patient Population

Among 1682 patients registered in the REALITY-AHF study, 85 patients with in-hospital death and 569 patients without complete BNP measurements were excluded. In total, 1028 patients were finally included into the analysis (Fig. 1).

Mean age of included patients was 77 ± 13 years and 57% were male. Mean left ventricular ejection fraction was 47 ± 16%. Median (interquartile range) of BNP level on admission and BNP at discharge were 474 ng/L (439−1367 ng/L) and 286 ng/L (146−504 ng/L), respectively. Median interval between two BNP measurements was 14 (9−22) days. Median and interquartile range of percentage BNP reduction was 62.5% (36.5−78.5%). The percentage BW change was 7.2% (3.6−11.1%). The correlation between percentage BNP reduction and percentage BW reduction was significant ($P<$ .001), but very weak (Spearman's rho = 0.122).

Table 1 summarizes patients' characteristics by percentage BNP quartile groups. Quartile 1 indicates patients with smallest percentage BNP reduction. As shown, BNP level on admission and at discharge were both significantly different among the groups ($P<$ .001 for both) and contributed to the difference in BNP reduction: BNP on admission was higher in patients with greater percentage BNP reduction and BNP at discharge was higher in patients with smaller BNP reduction. Patients with smaller percentage BNP reduction were prone to be older, had higher prevalence of past history of HF and atrial fibrillation, had lower prescription rate of angiotensin-converting-enzyme inhibitor, and demonstrated lower hemoglobin level. MAGGIC score was higher in patients with smaller BNP reduction. Physical examination findings such as peripheral edema, and jugular vein distention were not significantly different among the quartiles at either admission or discharge. Although the echocardiographic inferior vena cava and right ventricle-right atrium pressure gradients were not significantly different among quartiles on admission, the reduction during index hospitalization was significantly greater in the group with greater percentage BNP reduction, which supports the association of greater BNP reduction with successful decongestion. Diuretic response was significantly better in the patients with higher BNP reduction. The echocardiographic inferior vena cava and right ventricle-right atrium pressure gradients were smaller in the patients with greater BNP reduction, which suggests better decongestion. Other clinical characteristics, including sex, blood pressure, renal function, and sodium level were not significantly different among the groups.

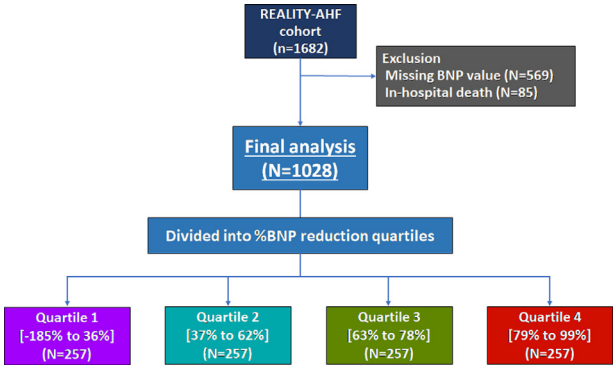

Fig. 1. Study flow chart. A total of 1028 patients were included in the final analysis and classified into quartiles of percentage BNP reduction.

Percentage BNP Reduction and Outcomes

During the 1-year follow-up period, 152 patients (14.8%) reached the primary endpoint of all-cause death and 235 patients (22.9%) were rehospitalized because of HF. Kaplan−Meier curve analyses showed that the group with smaller percentage BNP reduction was associated with higher rate of all-cause death ($P<$ .001) and composite endpoint ($P<$ .001). Event rate of smallest BNP reduction quartile was more than 2-fold higher for both all-cause death (23.0% vs 9.7%, $P<$ .001) and composite endpoint (44.7% vs 19.5%, $P<$ .001) than that of the greatest BNP reduction quartile (Fig. 2).

ROC analyses showed that percentage BNP reduction significantly predicts 1-year all-cause death (AUC 0.63, 95% confidence interval [CI] 0.58−0.68) and composite endpoint as well (AUC 0.63, 95% CI 0.60−0.67). In contrast, percentage BW reduction significantly predicted the composite endpoint (AUC 0.56, 95% CI 0.52−0.59), but not all-cause death (AUC 0.53, 95% CI 0.48−0.58). Comparing these two metrics, percentage BNP reduction had significantly greater AUCs than percentage BW reduction in predicting both outcomes ($P=$ .009 for all-cause death and $P=$ .004 for the composite endpoint; Fig. 3).

The results of multivariate Cox regression analyses are summarized in Table 2 and revealed that the percentage BNP reduction was significantly associated with all-cause death even after adjustment for the preexisting risk markers,

Table 1. Patient Characteristics

Variables	Quartile 1 [−185% to 36%] (n = 257)	Quartile 2 [37% to 62%] (n = 257)	Quartile 3 [63% to 78%] (n = 257)	Quartile 4 [79% to 99%] (n = 257)	*P* value
Age, y	78 ± 12	80 ± 11	77 ± 12	74 ± 15	<.001
Male sex, n (%)	135 (52.5)	144 (56.0)	156 (60.7)	151 (58.8)	.27
Systolic blood pressure (mmHg)	114 ± 19	114 ± 18	115 ± 16	115 ± 18	.87
Diastolic blood pressure (mmHg)	62 ± 11	61 ± 11	62 ± 11	63 ± 12	.072
Heart rate (/min)	72 ± 14	71 ± 14	69 ± 12	68 ± 12	.001
Body weight at admission (kg)	56.9 ± 15.4	56.7 ± 13.5	58.5 ± 16.6	59.9 ± 18.7	.081
Body weight at discharge (kg)	52.5± 13.7	52.5 ± 12.4	53.5 ± 14.9	54.2 ± 16.2	.49
NYHA class ≥III at discharge, n (%)	25 (9.9)	18 (7.1)	10 (3.9)	16 (6.3)	.064
ECG findings at discharge, n (%)					<.001
Sinus rhythm	129 (51.0)	135 (52.7)	153 (60.0)	199 (78.3)	
Atrial fibrillation	104 (41.1)	91 (35.5)	63 (24.7)	37 (14.6)	
Others	20 (7.9)	30 (11.7)	39 (15.3)	18 (7.1)	
LVEF, (%)	49 ± 17	49 ± 16	44 ± 14	46 ± 16	<.001
Past medical history, n (%)					
Heart failure	150 (58.4)	135 (52.5)	134 (52.1)	103 (40.1)	<.001
Hypertension	166 (64.6)	178 (69.3)	180 (70.3)	179 (69.9)	.47
Diabetes mellitus	97 (37.7)	98 (38.1)	102 (39.7)	82 (32.0)	.29
COPD	18 (7.0)	35 (13.6)	27 (10.5)	27 (10.6)	.11
Coronary artery disease	81 (31.6)	74 (28.8)	93 (36.2)	71 (27.7)	.16
Peripheral artery disease	30 (11.7)	14 (5.4)	17 (6.6)	21 (8.2)	.054
Atrial fibrillation	123 (47.9)	124 (48.2)	89 (34.6)	73 (28.4)	<.001
Smoking	93 (36.2)	95 (37.1)	109 (42.7)	108 (42.4)	.29
Prescription at discharge, n (%)	157 (61.8)	142 (55.9)	133 (52.0)	96 (37.6)	<.001
ACE inhibitor/ARB	138 (55)	158 (62)	182 (71)	187 (74)	<.001
Beta blocker	183 (71.5)	182 (71.1)	196 (76.6)	187 (74.5)	.45
Aldosterone blocker	117 (45.5)	123 (48.0)	126 (49.0)	112 (44.1)	.66
Statin	106 (41.2)	106 (41.4)	112 (43.6)	87 (34.1)	.14
Loop diuretics (furosemide equivalent, mg)	40 [20−40]	30 [20−40]	20 [20−40]	20 [10−30]	<.001
Physical examinations at admission, n (%)					
Peripheral edema	179 (69.6)	182 (70.8)	184 (71.6)	166 (64.6)	.31
Jugular vein distention	148 (58.0)	142 (55.7)	154 (60.4)	147 (57.6)	.76
Orthopnea	152 (59.4)	156 (60.9)	154 (60.2)	150 (58.4)	.94
Physical examinations at discharge, n (%)					
Peripheral edema	22 (8.8)	15 (6.0)	18 (7.2)	14 (5.6)	.49
Jugular vein distention	5 (2.0)	5 (2.0)	4 (1.6)	2 (0.8)	.68
Orthopnea	2 (0.8)	0 (0.0)	1 (0.4)	0 (0.0)	.29
Laboratory data					
WBC (/μL)	5600 [4400−7000]	5800 [4600−7000]	5800 [4700−7300]	5600 [4420−6800]	.22
Hemoglobin (mg/dL)	11.4 ± 2.1	11.6 ± 2.1	11.8 ± 2.2	12.0 ± 2.3	.003
AST (U/L)	22 [18−29]	22 [18−29]	22 [17−29]	21 [17−29]	.38
ALT (U/L)	16 [11−25]	16 [12−24]	16.50 [11−25]	17 [11−27]	.83
Creatinine (mg/dL)	1.2 [1.0−1.6]	1.2 [0.9−1.6]	1.2 [0.9−1.7]	1.1 [0.9−1.6]	.18
eGFR (mL/min/1.73 m^2)	49 [37−69]	52 [37−70]	53 [35−74]	58 [37−80]	.059
BUN (mg/dL)	26.10 [18−39.10]	26 [20−37]	26.40 [19−38]	25.50 [18.20−35.10]	.63
Sodium (mEq/L)	139 ± 5	139 ± 4	139 ± 4	139 ± 4	.92
BNP on admission (ng/L)	578 [322−907]	667 [381−1034]	801 [482−1545]	1150 [635−2048]	<.001
BNP at discharge (ng/L)	503 [335−837]	315 [188−501]	238 [138−440]	127 [68−255]	<.001
Diuretic response (first 6 hours), mL/40mg	1373 [703−2255]	1525 [780−2330]	1536 [960−2800]	1735 [903−2990]	.027
Diuretic response (first 48 hours), mL/40mg	2402 [1382−3802]	2257 [1522−3484]	2617 [1657−4006]	2813 [1682−4897]	.008
RV-RA pressure gradient on admission, mmHg	38.8 ± 14.1	38.9 ± 13.6	38.7 ± 14.0	38.5 ± 13.7	.99
RV-RA pressure gradient at discharge, mmHg	33.0 ± 13.5	31.2 ± 11.3	28.4 ± 12.0	27.1 ± 10.3	<.001
Change in RV-RA pressure gradient, mmHg	−6.2 ± 12.1	−7.4 ± 14.5	−9.4 ± 15.0	−11.0 ± 13.6	<.001
Inferior vena cava diameter on admission, mm	18.9 ± 4.9	18.7 ± 4.6	18.5 ± 4.7	19.1 ± 4.6	.55
Inferior vena cava diameter at discharge, mm	17.0 ± 5.1	15.2 ± 4.8	14.3 ± 5.6	13.7 ± 4.4	<.001
Changes in Inferior vena cava diameter, mm	−2.1 ± 4.2	−3.7 ± 5.5	−4.1 ± 5.2	−5.7 ± 5.3	<.001
MAGGIC Score	25.8 ± 6.7	25.1 ± 6.3	24.7 ± 6.2	22.5 ± 7.6	<.001
Hospital length (days)	17 [11−28]	16 [11−24]	17 [12−23]	20 [13−29]	<.001

ECG, electrocardiogram; COPD, chronic obstructive pulmonary disease; ACE, angiotensin convert enzyme; ARB, angiotensin II receptor blocker; WBC, white blood cell count; AST, aspartate transaminase; ALT, alanine transaminase; eGFR, estimated glomerular filtration rate; BUN, blood urea nitrogen; RV, right ventricle; RA, right atrium.

including BNP level at discharge and percentage BW reduction (hazard ratio [HR] 0.96, 95% CI 0.93−0.99, *P*= .032), and also after adjustment for MAGGIC score and BNP level at discharge (HR 0.96, 95% CI 0.92−0.99, *P*= .045). The association of percentage BNP reduction with the composite endpoint of all-cause death and HF readmission after adjustment for MAGGIC score and BNP level at discharge (HR 0.97, 95% CI 0.94−0.99, *P*= .033) was still significant, whereas that after adjustment for those risk factors had marginal *P* value (HR 0.97, 95%

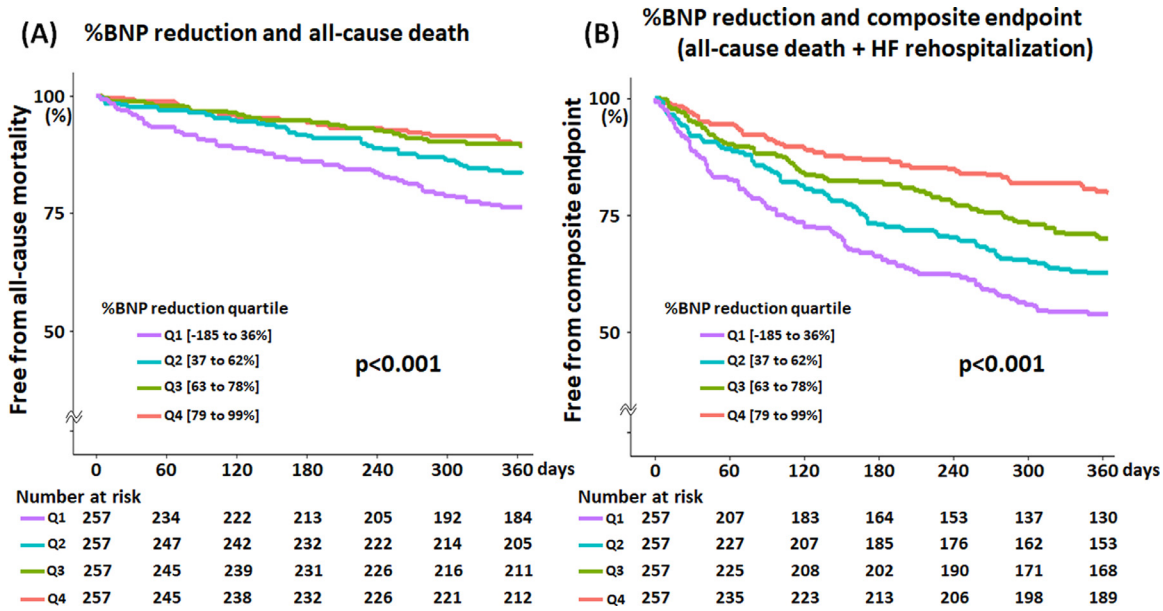

Fig. 2. Kaplan−Meier curves in percentage BNP reduction quartiles. (A) and (B) show the event-free survival rate for the all-cause death and the composite of all-cause death and hospitalization due to heart failure, respectively. Significant trends toward higher event rate were detected in the group with smaller percentage BNP reduction.

CI 0.95−1.00, *P*= .052). For both endpoints, percentage BW reduction did not show significant association when it was added to the model that included percentage BNP reduction (HR 1.00, 95% CI 0.77−1.31, *P*= .99 for 1-year all-cause death, and HR 0.86, 95% CI 0.73−1.02, *P*= .74 for the composite endpoint). HRs and 95% CIs for other covariates were summarized in Supplemental Table 1.

Results were still significant when Cox regression analyses were performed using multiple imputation (HR 0.97, 95% CI 0.94−0.99, *P*= .032 for 1-year all-cause death, and HR 0.98, 95% CI 0.96−0.96, *P*= .010 for the composite endpoint; Supplemental Table 2), and again, percentage BW reduction was not associated with 1-year all-cause death or combined death and HF rehospitalization when percentage BW reduction was added to the model including percentage BNP reduction (HR 0.99, 95% CI 0.99−1.00, *P*= .66 for 1-year all-cause death, and HR 0.99, 95% CI 0.99−1.00, *P*= .19 for the composite endpoint). After adding diuretic response in our models, percentage BNP reduction remained significant for all-cause death, whereas the *P*

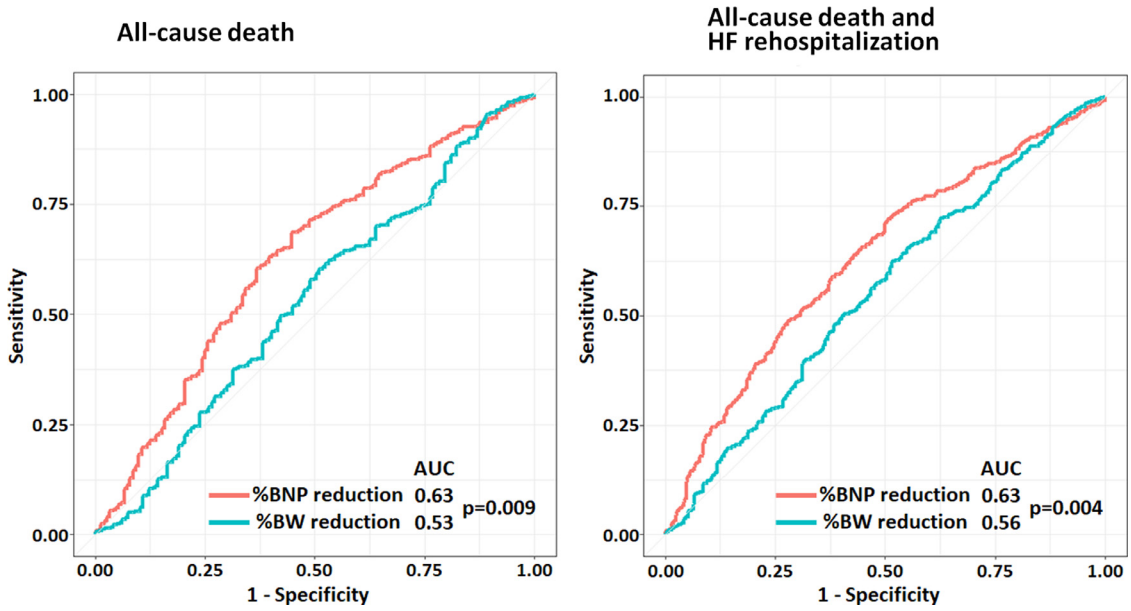

Fig. 3. Comparison between AUCs. These ROC curves compare the AUC of percentage BNP reduction with that of percentage BW reduction. Left shows the association with all-cause death, whereas the right shows the association with the composite events. Percentage BNP reduction had significantly stronger association with both endpoints.

Table 2. Cox Regression Models

	Univariate Cox Regression			Multivariate Cox Regression Adjusted for Risk Factors* + Percentage BW Reduction			Multivariate Cox Regression Adjusted for MAGGIC + BNP at Discharge			Multivariable Cox Regression Adjusted for Risk Factors* + BNP at Discharge + Diuretic Response		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
A. Models for all-cause death												
Percentage BNP change from baseline (per 10% decrease)	0.94	0.92−0.96	<.001	0.96	0.93−0.99	.032	0.96	0.92−0.99	.045	0.95	0.91−0.99	.007
B. Models for the composite endpoint of all-cause death and rehospitalization due to heart failure												
Percentage BNP change from baseline (per 10% decrease)	0.95	0.93−0.97	<.001	0.97	0.95−1.00	.052	0.97	0.94−0.99	.033	0.98	0.95−1.00	.13

*Age, sex past history of heart failure, diabetes mellitus, ischemic etiology, prescription of angiotensin-converting-enzyme inhibitor or angiotensin II receptor blocker, prescription of beta blocker, NYHA class, systolic blood pressure, hemoglobin, blood urea nitrogen, serum sodium level, estimated glomerular filtration rate, and BNP level

value for composite endpoint did not reach a statistically significant level (P= .13). The smooth HR plot showed that the adjusted HRs for all-cause death and the composites of all-cause death and rehospitalization were higher in the patients with lower BNP reduction and decreased especially in the patients with 50% or higher BNP reduction (Supplemental Fig. 3).

The incremental value of the percentage BNP reduction in addition to the baseline model was assessed using AUC and NRI. Although AUC significantly increased by adding the percentage BNP reduction (0.81−0.81 for all-cause death and 0.77−0.77 for the composite endpoint), NRI showed significant improvement of the models for both endpoints (0.30, P< .001 for all-cause death and 0.17, P= .001 for the composite endpoint).

In this study, BNP on discharge was measured more than 3 days before discharge in 26% of the patients. When limiting the cohort to those with BNP level measured within 3 days of discharge, the results remained the same; the percentage BNP reduction was still significantly predictive, whereas the percentage BW change was not (data not shown). Furthermore, we divided the patients into the group whose BNP at discharge was obtained within 24 hours of discharge (n = 411) and those with BNP measured before 24 hours of discharge (n = 552) to confirm if the predictive ability of percentage BNP reduction was different between the two groups. In the former group, AUC of percentage BNP reduction for predicting all-cause death and the composite endpoint were 0.68 (95% CI 0.61−0.76) and 0.65 (95% CI 0.59−0.70), whereas in the latter group, they were 0.60 (95% CI 0.53−0.66) and 0.62 (95% CI 0.57−0.67), respectively. P values for interaction showed no interaction between the predictive ability of percentage BNP change and whether BNP at discharge was measured within 24 hours or not in our present population (0.80 for all-cause death and 0.62 for the composite endpoint, respectively).

Percentage BNP Reduction in HFrEF and HFpEF

We further evaluated the interaction between left ventricular ejection fraction (LVEF) and prognostic impact of BNP reduction. There were 331 (35%) patients with HF with preserved ejection fraction (HFpEF; LVEF $\geq$ 50%), 200 (21%) patients with HF with midrange ejection fraction, and 408 (44%) patients with HF with reduced ejection fraction (HFrEF; LVEF < 40%). Compared with patients with HFrEF, patients with HFpEF had slightly, but significantly, smaller percentage BNP reduction (57.3% [32.7−77.3%] vs 67.3 [42.0−80.7%] for HFpEF and HFrEF, respectively). In patients with HFrEF, AUC of the percentage BNP reduction for predicting all-cause death (0.65, 95% CI 0.59−0.71) and composite endpoint (0.64, 95% CI 0.54−0.74) were both significant. In contrast, in patients with HFpEF, AUC for the composite endpoint was significant (0.61, 95% CI 0.55-0.67), but that for all-cause death was not (0.56, 95% CI 0.49−0.64: Supplemental Fig. 1). Exploratory analysis using smooth AUC plots

showed that as LVEF increased, AUC for predicting all-cause death decreased, while AUC for predicting the composite endpoint seemed relatively constant (Supplemental Fig. 2).

Discussion

In this study, we analyzed 1028 patients with AHF from REALITY-AHF and showed that 1) the correlation between percentage BNP reduction with percentage BW reduction during hospitalization was weak; 2) percentage BNP reduction performed better than BW reduction in predicting both 1-year all-cause death and the combined endpoint of all-cause death and HF rehospitalization; 3) percentage BNP reduction had a significant association with all-cause death and the composite endpoints independent of other important covariates, including BNP levels at discharge and percentage BW reduction; and 4) predictive ability of percentage BNP reduction for all-cause death was greater in patients with HFrEF compared with HFpEF. To date, this is the largest study investigating the impact of BNP reduction during HF hospitalization in addition to baseline BNP level and the first study showing the superiority of percentage BNP reduction over percentage BW reduction. Although many prognostic markers have been used, risk prediction in HF is still challenging and is not accurate enough, with C-statistics of ~0.75 in large studies and meta-analyses.[33,34] Therefore, risk prediction models still need to be improved. Our current results showed significant improvement of risk stratification by adding BNP reduction to the known risk predictors, which suggests that BNP reduction has a potential to improve clinical risk prediction for HF.

Because congestion is the primary cause of worsening HF in most cases, decongestion using diuretics is the main therapeutic strategy during AHF hospitalization.[4–6] However, the assessment of adequate decongestion has remained a challenge for physicians. The sensitivity and specificity of physical examination to detect elevated left ventricular filling pressure are unsatisfactory and there is a concern in reproducibility and interobserver variability.[35,36] Net urine output is one of the options recommended in the guidelines; however, it is difficult to assess net urine output in all patients through hospitalization and there is a concern that the parameter does not consider insensible perspiration. BW reduction is also recommended in the guidelines and may be an easier and more reproducible measurement of decongestion. In the present study, however, the correlation between percentage BW reduction and percentage BNP reduction was weak and the prognostic ability of percentage BW reduction was limited and significantly lower than that of percentage BNP reduction. This might be because the change in BW mostly comes from the simple change in fluid volume, whereas change in BNP reflects not only volume reduction, but also hemodynamic improvement and optimization in patients with AHF.

BNP level has been reported to change dramatically as a reflection of changes in LV filling pressure and the most rapid changes were detected during hospitalization,[13,14] whereas baseline BNP level in stable chronic HF ranges widely and depends not only on LV filling pressure and HF severity, but also on body size, renal function, age, sex, race, arrhythmia, etc.[37–41]. Some studies have reported that an absolute threshold of BNP level at discharge is associated with clinical outcome.[12,42–44] Kociol et al. showed that BNP level at discharge had stronger association with the outcome than admission/discharge BNP ratio.[12] This result is not contradictory to ours, because BNP level at discharge seems to be affected by the baseline BNP levels before the indexed deterioration, which reflect more comprehensive patient characteristics rather than the effect of treatment during the indexed hospitalization. Unique from these previous reports, we show that percentage BNP reduction, as a pure effect of treatment during the indexed hospitalization, was associated with prognosis independent of BNP levels at discharge. The obtained result was robust, because another model using MAGGIC score, which is an established risk score calculated by many parameters, also showed an independent association between smaller BNP reduction and worse clinical outcomes. Another model using multiple imputation and including all the patients (1682 patients) also supported the results. Therefore, even in patients with low BNP level at discharge, percentage BNP reduction during hospitalization should be carefully assessed.

An important question arising from these results is whether we can improve the clinical outcome by referring to BNP levels. Felker et al[15] randomized ~900 patients with chronic HF to usual care or NTproBNP-guided therapy, in which HF therapy was titrated to achieve a target NTproBNP level of <1000 pg/mL. They found no difference in outcomes between the two arms. More recently, a multicenter randomized control trial failed to show the superiority of a therapeutic strategy targeting a NTproBNP reduction of >30% during AHF hospitalization compared with the conventional treatment.[17] However, patients who achieved a NTproBNP reduction of >30% with the intervention had better outcomes than those who did not. Although the difference did not reach statistical significance, it is probably because of the small sample size (only 67 patients underwent the intervention, of who 32 achieved NTproBNP reduction). Thus, effective use of natriuretic peptide as therapeutic guidance is yet to be elucidated. Our study confirms the close association of percentage BNP reduction with clinical outcome in a large sample size and provides new insights such as the difference between HFpEF and HFrEF, which will be useful in conducting future investigations.

In the present analysis, the predictive ability of percentage BNP reduction for all-cause death was greater in patients with HFrEF compared with those with HFpEF. Patients with HFpEF have been reported to have lower BNP levels and more various comorbidities compared those with HFrEF.[45–47] A randomized control trial by Maeder et al[47] reported that NTproBNP guide therapy was effective

in HFrEF, but not in HFpEF. Although we currently do not have enough data to explain this difference, a possible explanation of this phenomenon is that patients with HFpEF have more comorbidities than those with HFrEF and, therefore, die of non-cardiac causes. This hypothesis is supported by the fact that percentage BNP reduction was predictive even in HFpEF for the composite of heart failure admission and all-cause death, which comprise more cardiac events. Further studies are warranted to establish in-hospital assessment of successful treatment in HFpEF.

Study Limitations

This study has some limitations. This was a retrospective analysis of a registry. We used multiple multivariate models, including a number of risk markers and a well-established risk score, to adjust for confounders as much as possible and the results were significant for both primary and secondary endpoints after adjustment for these models. However, there remains a possibility that unadjusted confounding factors affected our results. Because this study was performed in Japan, where hospitalization length for AHF is generally longer than that in the United States and Europe, it may be associated with relatively greater BNP reduction shown in this study compared with that in previous studies, and the results may not be identically applicable to other countries. In this study, physicians were not blinded to BNP level, and the study protocol did not include any criteria for patient discharge; accordingly, BNP level on discharge might have influenced the physicians' decisions on timing of discharge. It should be acknowledged that we had to exclude a considerable number of patients because of lack of data on BNP levels at either admission or discharge. Compared with the study population, these excluded patients had some differences in patient characteristics including, slightly, but significantly, higher MAGGIC score and significantly worse outcomes (data not shown). Although this finding might also reinforce the importance of BNP measurement at discharge, this point should be taken as one of the important limitations of the present study, even though we attempted to determine whether missing data significantly impacted our results using the multiple imputation technique and found consistent results. Finally, the present study was not conducted to reveal the mechanisms and cause−result relationships. Further studies are warranted to investigate the underlying mechanisms.

Conclusions

In conclusion, the prognostic value of percentage BNP reduction during hospitalization was superior to that of percentage BW reduction and was independent of other risk markers including BNP at discharge.

Disclosures

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Supplementary materials

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