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Relation of Decongestion and Time to Diuretics to Biomarker Changes and Outcomes in Acute Heart Failure

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Prompt treatment may mitigate the adverse effects of congestion in the early phase of heart failure (HF) hospitalization, which may lead to improved outcomes. We analyzed 814 acute HF patients for the relationships between time to first intravenous loop diuretics, changes in biomarkers of congestion and multiorgan dysfunction, and 1-year composite end point of death or HF hospitalization. B-type natriuretic peptide (BNP), high sensitivity cardiac troponin I (hscTnI), urine and serum neutrophil gelatinase−associated lipocalin, and galectin 3 were measured at hospital admission, hospital day 1, 2, 3 and discharge. Time to diuretics was not correlated with the timing of decongestion defined as BNP decrease ≥ 30% compared with admission. Earlier BNP decreases but not time to diuretics were associated with earlier and greater decreases in hscTnI and urine neutrophil gelatinase−associated lipocalin, and lower incidence of the composite end point. After adjustment for confounders, only no BNP decrease at discharge was significantly associated with mortality but not the composite end point ($p = 0.006$ and $p = 0.062$, respectively). In conclusion, earlier time to decongestion but not the time to diuretics was associated with better biomarker trajectories. Residual congestion at discharge rather than the timing of decongestion predicted a worse prognosis. **(Am J Cardiol 2021;147:70−79)**

In patients with acute heart failure (AHF), prompt initiation of decongestive therapy may help mitigate the adverse effects of congestion and multi-organ injury in the early phase of hospitalization and result in improved outcomes. Several studies have examined the relationship between early initiation of diuretics and/or vasoactive agents and clinical outcomes.[1-4] However, a pathophysiologic link between early treatment, decongestion, organ damage and clinical outcomes has not been fully assessed, especially from the viewpoint of biomarker trajectories. B-type natriuretic peptide (BNP) is a well-established biomarker of congestion and the timing of BNP decrease can serve as an objective surrogate for time to decongestion.[5] In this subanalysis of the Acute Kidney Injury Neutrophil gelatinase−associated lipocalin (NGAL) Evaluation of Symptomatic heart failure Study (AKINESIS), we investigated whether

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(1) early diuretic therapy results in early decongestion, defined by a decrease in BNP, (2) early diuretic therapy versus decongestion correlates with favorable biomarker changes, and (3) early diuretic therapy versus decongestion is associated with better clinical outcomes.[6]

Methods

We retrospectively analyzed patients enrolled in the AKINESIS.[6] AKINESIS was a prospective, international, multicenter cohort study of AHF patients, which enrolled 927 AHF patients at 16 sites in the United States and Europe from January 2011 through September 2013. The study methods have been previously described.[6] Briefly, subjects with symptoms and signs of AHF and having received or planned administration of intravenous diuretic therapy were enrolled. In the current analysis, we excluded 70 patients discharged from the emergency department, 28 patients without BNP data on admission, and 15 patients lacking serial BNP measurements, leaving 814 patients for this analysis.

Time to diuretics was defined as the time from presentation to the first intravenous loop diuretic administration. Time to BNP decrease was defined as the day when BNP decreased by ≥ 30% compared with admission and the last BNP value was also ≥ 30% lower than admission.[7-10] Serum and urine specimens for biomarker assessment were tested at 5 time-points if the participant remained hospitalized for the duration of collection times: (1) day of enrolment within 2-hour of first diuretic administration; (2) hospital day 1; (3) hospital day 2; (4) hospital day 3, and (5) the day of discharge or anticipated discharge. Biomarkers analyzed, in addition to BNP, were high sensitivity cardiac troponin I (hscTnI), urine and serum NGAL (uNGAL and sNGAL) and galectin 3 (Gal3). Details of biomarker assessment were reported in elsewhere.[11] uNGAL was indexed to urine creatinine to account for urine tonicity. Levels of serum creatinine were measured each day during hospitalization.

The primary outcome was a 1-year composite of death or HF hospitalization. In-hospital, 1-year mortality and 1-year HF hospitalization were analyzed as secondary outcomes.

Patient characteristics were evaluated stratifying time to diuretics and BNP decrease with analysis of variance, Kruskal−Wallis or chi-square test as appropriate. Time to diuretics was compared by the time to BNP decrease both as a continuous variable and dichotomized as before or after 60 minutes.[3] Loop diuretic equivalents were converted with 1 mg bumetanide = 20 mg torsemide = 40 mg furosemide for intravenous doses and 1 mg bumetanide = 20 mg torsemide = 80 mg furosemide for oral doses.[12,13] Relative changes of biomarkers from admission to each sample collection were compared stratifying quartiles of time to diuretics and time to BNP decrease with Kruskal−Wallis test. Kaplan-Meier, log-rank and Cox regression analysis were performed for 1-year outcomes. In multivariable Cox regression analysis, confounding factors were selected based on prior studies including age, African American race, history of chronic obstructive pulmonary disease , edema, systolic blood pressure , heart rate, sodium, hemoglobin, blood urea nitrogen (BUN) and hscTnI.[14-17] To investigate factors associated with BNP ≥ 30% decrease at day 1, and with BNP < 30% decrease at discharge, univariable and multivariable logistic regression analyses were performed. Factors with p-value < 0.05 in univariable analysis were included in the multivariable model. All biomarkers were log-2 transformed in Cox and logistic regression analyses. All statistical analyses were performed using R version 3.6.3 for Windows.

Results

The mean age of the 814 patients was 69 ± 14 years, 63% were male, 47% had a history of coronary artery disease (CAD), 44% had diabetes, and 26% reported a history of chronic kidney disease. Median creatinine was 1.20 mg/dl (interquartile ranges [IQR] 0.94 to 1.61 mg/dl) and median BNP was 569 ng/l (IQR 233 to 1108 ng/l). Median dose of intravenous furosemide equivalents within the first 3 days of hospitalization was 60 mg/day (IQR 40 to 100 mg/day). BNP decrease at day 1, 2, 3 and discharge were observed in 166 (20%), 148 (18%), 55 (6.7%), and 52 patients (6.4%), respectively. Patients with earlier BNP decrease were younger, more likely to be non-white race, less frequently had a history of chronic kidney disease and had jugular vein distention on admission (Table 1). They had higher systolic blood pressure, and lower levels of creatinine and Gal3 on admission. The prevalence of CAD and interventions were not different between the groups.

The median time to first intravenous diuretics was 2.95 [IQR 1.75 to 5.78] hours. Patients in the earliest quartile of time to diuretic therapy (< 1.75 hours) were the oldest, had highest percentage of white race, and had the highest BUN on admission (Supplemental Table 1). Those with the latest quartile of time to diuretic therapy were most likely to be male and have rales. The dose of diuretic was not associated with the timing of the first dose. Although a numerical stepwise increase in time to diuretics was observed with BNP decrease at day 1 to discharge, no BNP decrease at discharge was also associated with shorter time to diuretics (Figure 1A). Receiving diuretics within 1 hour of the presentation was not correlated with the time to BNP decrease either (12% in patients with BNP decrease at day1, 11% in day 2, 8% in day 3, 13% in BNP decrease at discharge and 13% in no BNP decrease, p = 0.822). Urine output and changes in body weight were not correlated with time to diuretics (Figure 1B). Although there was some evidence of those with an earlier BNP decrease having an earlier and greater body weight decrease, this was not statistically significant (Figure 1C).

No relationship was observed regarding time to diuretics and change in biomarkers (Figure 2A). Patients with later time to diuretics had higher relative ratios of hscTnI, uNGAL, and sNGAL at discharge, though these findings were not statistically significant. In contrast, earlier BNP decrease was associated with earlier and greater decreases in hscTnI and uNGAL (Figure 2B). Creatinine increased more in earlier BNP decrease groups, and a similar finding was observed with sNGAL and Gal3.

In-hospital mortality was 3.3% (27 patients). Patients in earlier time to diuretic therapy had a numerically higher in-hospital mortality, but this was not statistically significance

Table 1
Baseline characteristics by time to B-type natriuretic peptide decrease

Variables	Day 1 n = 166	Day 2 n = 148	Day3 n = 55	At discharge n = 52	No Decrease n = 393	p-value
Age (years), mean±SD	65±14	66±14	68±12	71±14	71±14	<0.001
Non-white	73 (44%)	65 (44%)	22 (40%)	10 (19%)	124 (32%)	0.001
Men	103 (62%)	91 (62%)	37 (67%)	32 (62%)	247 (63%)	0.958
Coronary artery disease	70 (42%)	68 (46%)	30 (55%)	25 (48%)	193 (49%)	0.471
Myocardial infarction	44 (27%)	38 (26%)	18 (33%)	11 (21%)	111 (28%)	0.693
Percutaneous coronary intervention	32 (19%)	28 (19%)	11 (20%)	16 (31%)	93 (24%)	0.330
Coronary artery bypass grafting	23 (14%)	23 (16%)	14 (26%)	8 (15%)	73 (19%)	0.305
Hypertension	135 (81%)	124 (84%)	46 (84%)	37 (71%)	310 (79%)	0.306
Hyperlipidemia	84 (51%)	84 (57%)	29 (53%)	26 (50%)	197 (50%)	0.724
Diabetes mellitus	71 (43%)	66 (45%)	24 (44%)	27 (52%)	173 (44%)	0.843
Chronic obstructive pulmonary disease	45 (27%)	46 (31%)	11 (20%)	5 (10%)	102 (26%)	0.034
Chronic kidney disease	27 (16%)	40 (27%)	9 (16%)	20 (39%)	117 (30%)	0.001
Smoker	31 (19%)	24 (16%)	12 (22%)	7 (14%)	53 (14%)	0.359
Angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker	52 (31%)	43 (29%)	23 (42%)	16 (31%)	122 (31%)	0.528
Beta-blockers	123 (74%)	108 (73%)	39 (71%)	42 (81%)	270 (69%)	0.352
Diuretic agents	118 (71%)	103 (70%)	40 (73%)	39 (75%)	276 (70%)	0.950
Loop diuretic dose within the first 3 days of hospitalization (mg/day), median [IQR]	60 [33, 80]	63 [40, 99]	67 [40, 103]	62 [40, 133]	60 [40, 107]	0.081
Edema	117 (71%)	110 (74%)	47 (86%)	35 (67%)	305 (78%)	0.087
Jugular vein distension	24 (15%)	40 (27%)	15 (27%)	21 (40%)	118 (30%)	0.001
Rales	66 (40%)	61 (41%)	27 (49%)	30 (58%)	177 (45%)	0.176
Systolic blood pressure (mm Hg), mean±SD	148±30	145±30	141±28	136±28	135±29	<0.001
Heart rate (beats/min), mean±SD	89±21	88±22	93±26	84±19	87±24	0.185
Sodium (mEq/l), median [IQR]	139 [137, 141]	139 [138, 142]	140 [137, 142]	140 [137, 142]	139 [136, 141]	0.001
Hemoglobin (g/dl), mean±SD	12.0±2.5	11.6±2.2	11.8±2.3	11.4±2.0	11.5±2.7	0.188
Blood urea nitrogen (mg/dl), median [IQR]	21.0 [16.0, 29.0]	23.0 [15.0, 32.5]	24.0 [16.0, 31.5]	33.0 [18.9, 58.3]	26.0 [18.3, 42.0]	<0.001
Creatinine (mg/dl), median [IQR]	1.10 [0.83, 1.36]	1.21 [1.00, 1.64]	1.17 [1.00, 1.50]	1.22 [1.05, 1.63]	1.25 [0.96, 1.70]	0.001
B-type natriuretic peptide (ng/l), median [IQR]	550 [268, 1065]	769 [313, 1260]	713 [252, 1168]	688 [371, 1268]	456 [195, 1027]	0.003
High-sensitivity cardiac troponin I (ng/l), median [IQR]	22.2 [11.8, 51.3]	24.1 [12.6, 62.1]	32.1 [17.1, 98.8]	27.5 [15.3, 56.0]	25.5 [12.5, 55.5]	0.229
Urine neutrophil gelatinase-associated lipocalin (ug/g), median [IQR]	23.2 [13.6, 57.8]	31.7 [12.9, 71.0]	26.8 [13.8, 54.2]	42.7 [16.3, 104.2]	25.7 [12.8, 70.0]	0.340
Serum neutrophil gelatinase-associated lipocalin (ng/ml), median [IQR]	121.4 [74.3, 196.4]	140.5 [77.4, 249.0]	119.7 [87.8, 227.8]	196.5 [101.3, 359.6]	146.7 [87.2, 247.5]	0.008
Galectin 3 (ng/ml), median [IQR]	22.8 [18.3, 30.7]	24.2 [19.2, 31.2]	23.3 [18.7, 29.9]	29.0 [22.3, 43.6]	27.9 [20.4, 41.2]	<0.001

IQR, Interquartile range; SD, standard deviation

(Figure 3A). Those without BNP decrease during hospitalization had the highest in-hospital mortality, but the timing of BNP decrease at day 1, 2 and 3 was not correlated with mortality Figure 3B. The 1-year composite end point was observed in 276 patients (34%), with 147 patients (18%) dying and 163 patients (20%) hospitalized because of HF. The earliest time to diuretics was associated with the highest risk of the composite end point and mortality in univariate analysis. These relationships were not statistically significant after adjustment for confounders. (Figure 4A and Table 2). There was a stepwise increase in risk for the composite end point and mortality in patients with later timing of decrease or no decrease of BNP compared with BNP decrease at day 1 (Figure 4B and Table 3). After adjustment for confounders, only no BNP decrease at discharge remained statistically significant for mortality but not for the composite end point.

In the multivariable logistic regression analysis, lack of jugular vein distension, higher systolic blood pressure and lower galectin 3 were associated with a higher odds of having BNP decrease at day 1 (Table 4). Older age, lower systolic blood pressure, lower sodium, lower BNP and higher galectin 3 were associated with a higher odds of having no BNP decrease at discharge (Table 5).

Discussion

Among AHF patients treated with intravenous diuretic therapy, time to diuretics was not correlated with time to BNP decrease, and earlier time to BNP decrease but not time to diuretics was associated with better biomarker trajectories. Although earlier BNP decreases were associated with a lower incidence of the composite end point, only no BNP decrease at discharge was an independent predictor of mortality, but not the composite end point.

Prompt initiation of decongestive therapy in AHF may theoretically mitigate the adverse effects of congestion including multi-organ dysfunction and injury in the early phase of hospitalization and is expected to result in better prognosis. However, prior studies have had variable

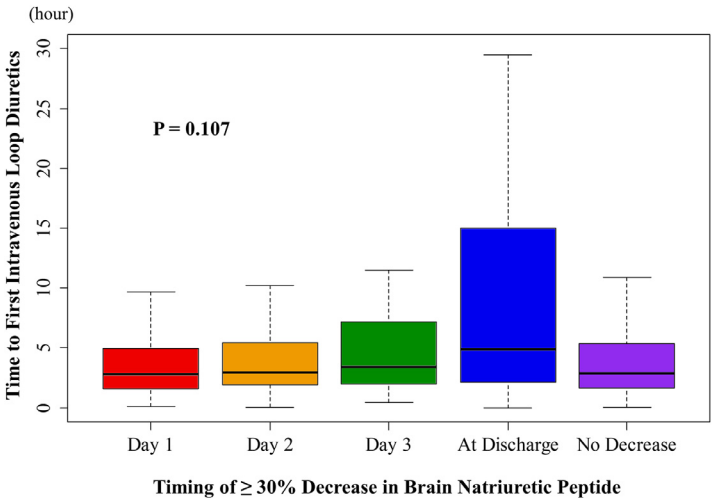
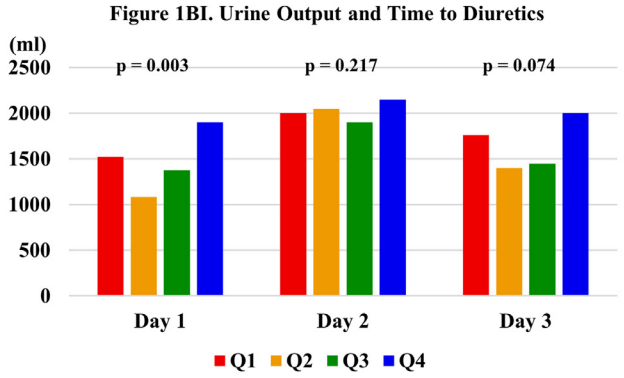
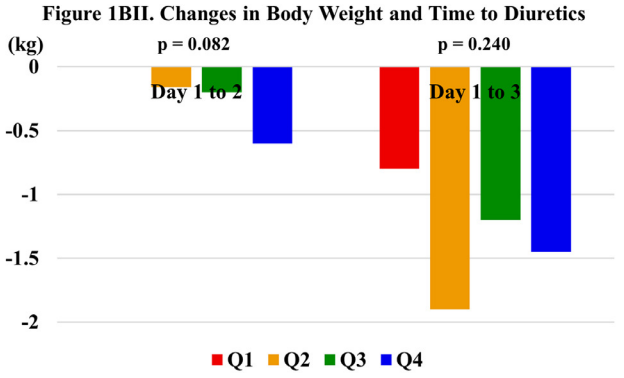
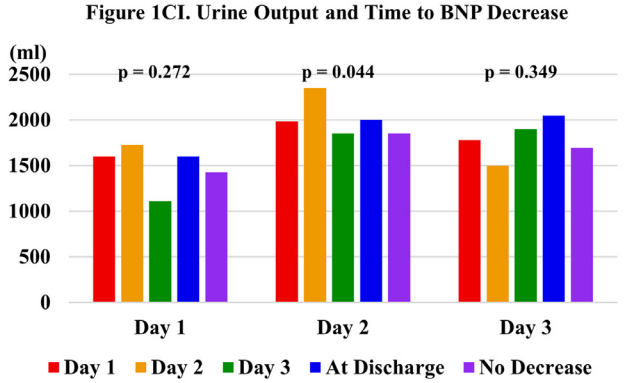


Figure 1A. Relationship between Time to Diuretics and B-type Natriuretic Peptide Decrease
Although a numerical stepwise increase in time to first intravenous diuretic dose was observed with BNP decrease at day 1 to discharge, no BNP decrease at discharge was also associated with shorter time to diuretics (p = 0.107). Time to BNP decrease was defined as the day when BNP decreased by ≥ 30% compared with admission and the last BNP value was also ≥ 30% lower than admission. BNP, B-type natriuretic peptide.

outcomes with not all supporting this hypothesis.[1-4] In our analysis, time to diuretic therapy was correlated with neither greater urine output, larger body weight decrease, earlier BNP decrease nor better trajectories of other pathophysiologic biomarkers. The earliest diuretic therapy group was associated with an increased risk of worse outcomes, and this relationship attenuated after adjustment for baseline characteristics suggesting these patients potentially had a profile of more severe decompensation of HF that prompted clinicians to treat earlier. AHF is a heterogeneous







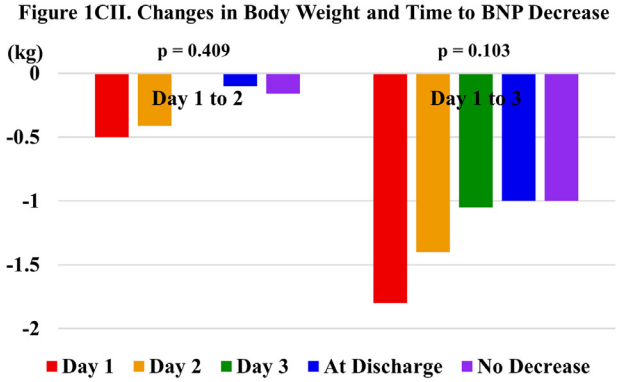


Figure 1B and 1C. urine output and changes in body weight by time to diuretics and B-type natriuretic peptide decrease. Urine output and changes in body weight were not correlated with time to diuretics (Figure 1B). Although there was some evidence of those with an earlier BNP decrease having an earlier and greater body weight decrease, this was not statistically significant (Figure 1C). BNP, B-type natriuretic peptide.

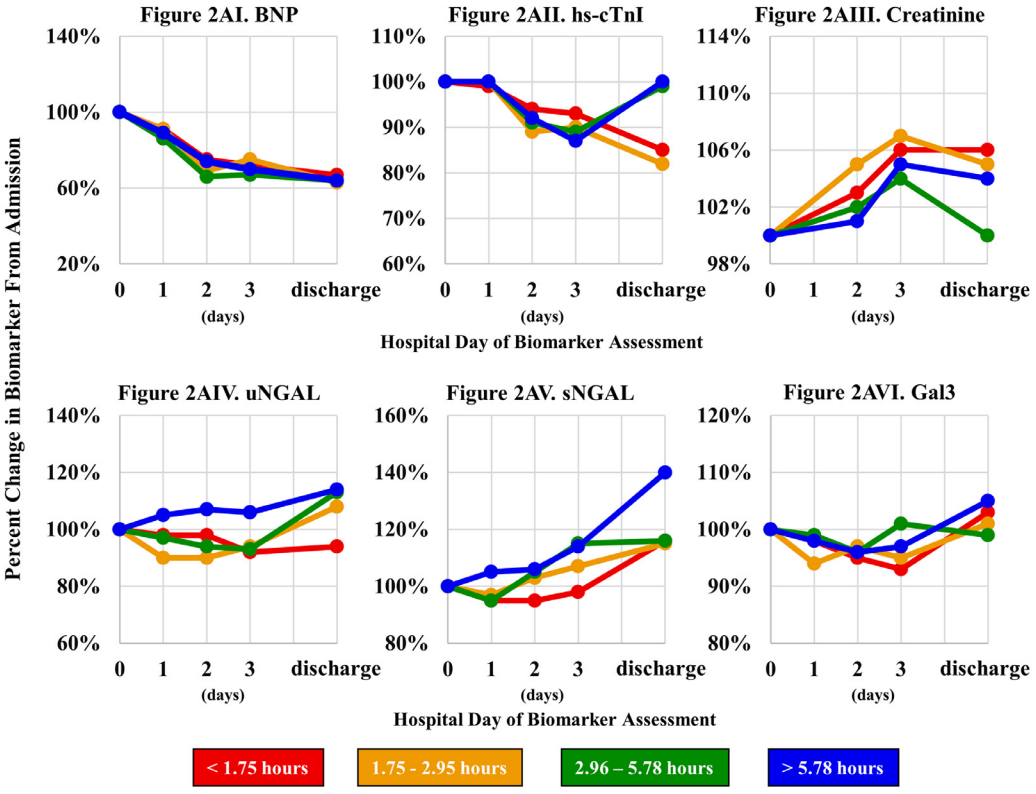


Figure 2A. Time to diuretics and biomarker changes. No relationship was observed between time to diuretics and change in biomarkers. Time to first intravenous loop diuretic; quartile 1 < 1.75 hours, quartile 2 1.75 to 2.95 hours, quartile 3 2.96 to 5.78 hours, and quartile 4 > 5.78 hours.

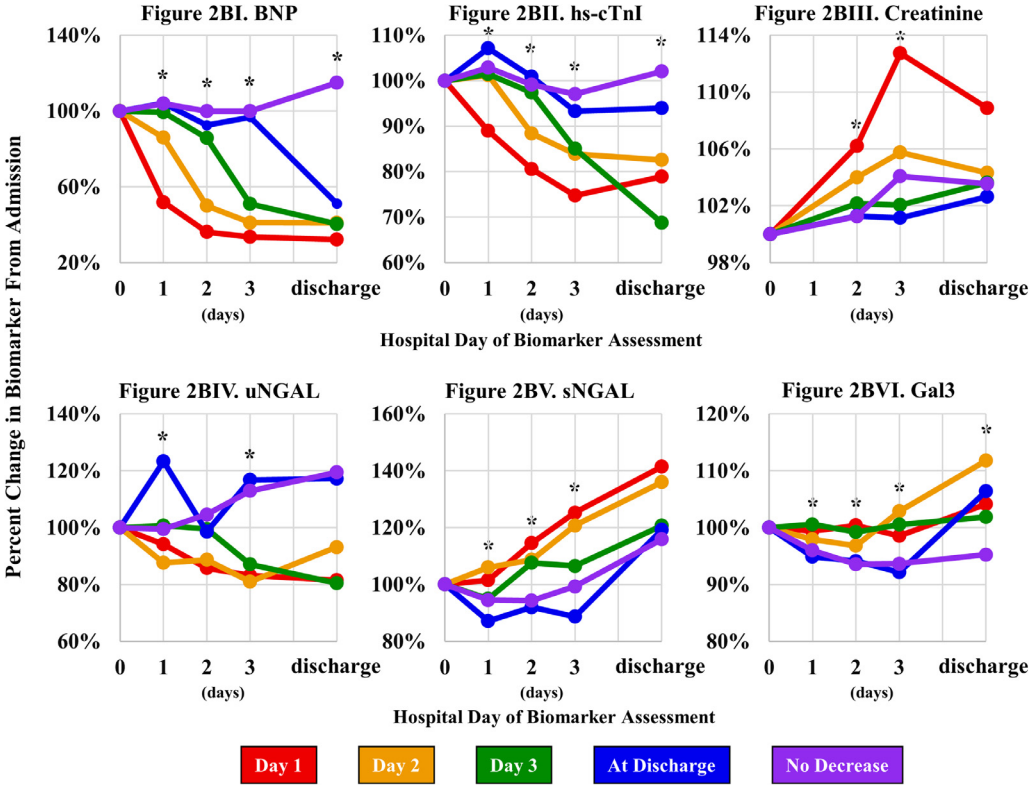


Figure 2B. Time to B-type natriuretic peptide decrease and biomarker changes. Earlier BNP decrease was associated with earlier and greater decreases in hscTnI and uNGAL (Figure 2BII and 2BIV). Creatinine increased greater in earlier BNP decrease groups, and a similar finding was observed with sNGAL and Gal3 (Figure 2BIII, 2BV and 2BVI). *p < 0.05.

BNP, B-type natriuretic peptide; Gal3, galectin 3; hscTnI, high sensitivity cardiac troponin I; sNGAL, serum neutrophil gelatinase−associated lipocalin; uNGAL, urine neutrophil gelatinase−associated lipocalin.

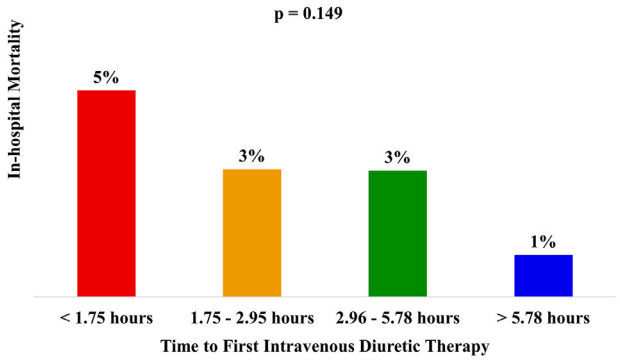


Figure 3A. In-hospital mortality and time to diuretics. Earlier time to diuretic therapy was associated with higher in-hospital mortality, but this did not reach statistical significance (p = 0.149).

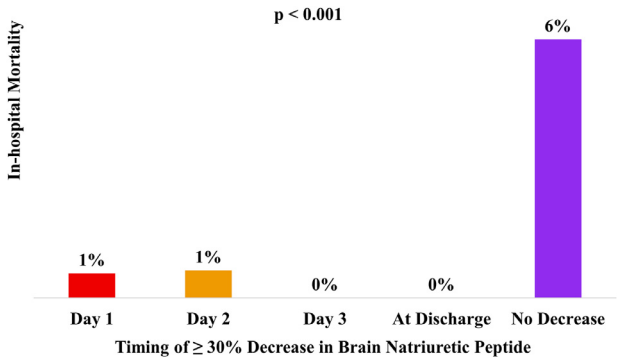


Figure 3B. In-hospital mortality and time to B-type natriuretic peptide decrease. Patients without BNP decrease during hospitalization had the highest in-hospital mortality, whereas the timing of BNP decrease at day 1, 2 and 3 was not associated with mortality (p < 0.001). BNP, B-type natriuretic peptide.

disease with complex pathophysiologic processes, various symptoms and disease severity, multiple co-morbidities, and several precipitating factors. These can significantly affect the timing of therapy initiation and may explain the inconsistent relationships between the timing of therapy and clinical outcomes in ours and previous studies.

We found an earlier BNP decrease was associated with earlier and greater decreases in hscTnI and uNGAL, and greater increases in creatinine, sNGAL and Gal3. The decrease in hscTnI in the earlier BNP decrease groups suggests faster resolution of myocardial damage with faster decongestion.[17,18] A rise in creatinine with decreases in BNP and uNGAL can reflect successful decongestive therapy with the development of renal functional deterioration, but without the occurrence of tubular damage.[7,19,20] It is remarkable that those groups with delayed or failed decongestion did not have serum creatinine increases, but did develop renal tubular damage (uNGAL increase), and had the highest mortality. sNGAL not only reflects kidney injury but also systemic inflammation, and Gal3 reflets inflammation and fibrosis.[19,21] Elevations of these biomarkers in earlier BNP decrease groups can be a result of decreased renal clearance rather than the activation of these pathophysiologic processes, considering concomitant creatinine elevation and better clinical outcomes in these groups.

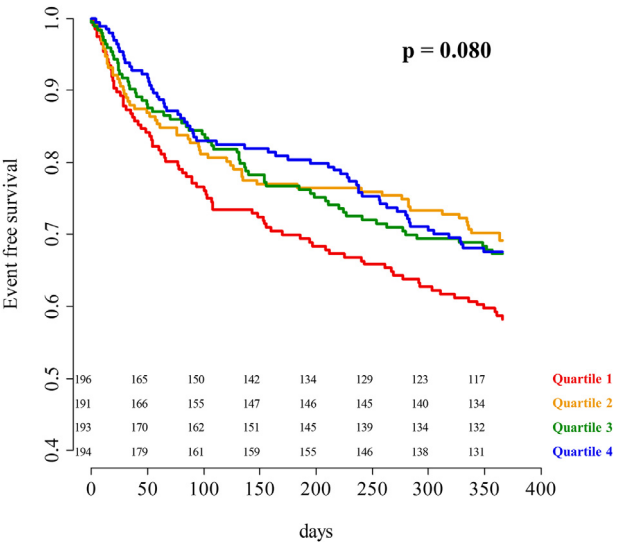


Figure 4A. Time to Diuretics and One-year Composite of Death or Heart Failure Hospitalization
There was a trend that patients with the earliest time to diuretics were associated with the highest risk of the composite end point of death or HF hospitalization (p = 0.080). Time to first intravenous loop diuretic; quartile 1 < 1.75 hours, quartile 2 1.75 to 2.95 hours, quartile 3 2.96 to 5.78 hours, and quartile 4 > 5.78 hours. HF, heart failure.

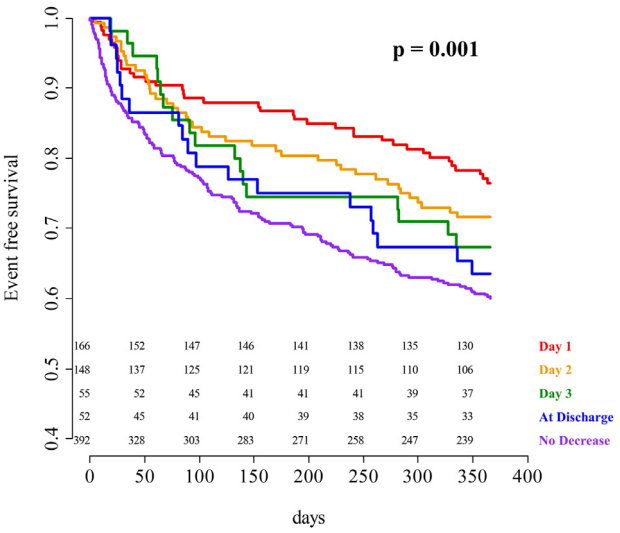


Figure 4B. Time to B-type natriuretic peptide decrease and one-year composite of death or heart failure hospitalization. There was a stepwise increase in risk for the composite end point in patients with later timing of decrease or no decrease of BNP compared with BNP decrease at day 1 (p = 0.001). BNP, B-type natriuretic peptide.

Intriguingly, these favorable biomarker changes were not translated into improved clinical outcomes in our analysis. Recent trials of novel vasoactive agents cast doubt on the beneficial effects of early treatment strategies and a pathophysiologic link between favorable biomarker changes and better outcomes.[22,23] In the RELAX-AHF trial, serelaxin provided an earlier decrease in N-terminal pro-BNP (NT-pro-BNP) and hscTnT, indicating its effect on faster decongestion and myocardial protection.[18] However,

Table 2A
Time to diuretics and one-year outcomes

Composite of mortality or HF hospitalization						
	Univariable			Multivariable		
	HR	95% CI	p-value	adjusted HR	95% CI	p-value
Quartile 1		reference			reference	
Quartile 2	0.69	0.49-0.96	0.029	0.74	0.52-1.04	0.083
Quartile 3	0.73	0.53-1.01	0.060	0.78	0.55-1.11	0.171
Quartile 4	0.71	0.51-0.98	0.039	0.72	0.51-1.02	0.064
Mortality						
	Univariable			Multivariable		
	HR	95% CI	p-value	adjusted HR	95% CI	p-value
Quartile 1		reference			reference	
Quartile 2	0.62	0.39-0.98	0.039	0.68	0.42-1.08	0.104
Quartile 3	0.66	0.42-1.03	0.067	0.84	0.52-1.36	0.485
Quartile 4	0.62	0.40-0.98	0.042	0.66	0.41-1.07	0.094
HF hospitalization						
	Univariable			Multivariable		
	HR	95% CI	p-value	adjusted HR	95% CI	p-value
Quartile 1		reference			reference	
Quartile 2	0.79	0.51-1.22	0.285	0.79	0.51-1.24	0.314
Quartile 3	0.81	0.53-1.24	0.326	0.77	0.49-1.22	0.271
Quartile 4	0.79	0.51-1.21	0.271	0.78	0.5-1.23	0.285

Table 2B. Time to B-type natriuretic peptide decrease and one-year outcomes

Composite of mortality or HF hospitalization						
	Univariable			Multivariable		
	HR	95% CI	p-value	adjusted HR	95% CI	p-value
Day 1		reference			reference	
Day 2	1.25	0.81-1.93	0.317	1.05	0.67-1.64	0.842
Day 3	1.46	0.84-2.56	0.181	1.23	0.70-2.17	0.469
At discharge	1.69	0.98-2.93	0.060	1.19	0.67-2.12	0.542
No BNP decrease	1.96	1.38-2.79	< 0.001	1.42	0.98-2.04	0.062
Mortality						
	Univariable			Multivariable		
	HR	95% CI	p-value	adjusted HR	95% CI	p-value
Day 1		reference			reference	
Day 2	1.55	0.73-3.28	0.252	1.17	0.55-2.52	0.683
Day 3	2.39	1.00-5.66	0.049	1.85	0.77-4.43	0.167
At discharge	3.10	1.37-7.02	0.007	1.80	0.77-4.21	0.175
No BNP decrease	3.93	2.16-7.16	< 0.001	2.38	1.29-4.38	0.006
HF hospitalization						
	Univariable			Multivariable		
	HR	95% CI	p-value	adjusted HR	95% CI	p-value
Day 1		reference			reference	
Day 2	1.08	0.65-1.8	0.770	0.99	0.59-1.66	0.956
Day 3	1.10	0.55-2.19	0.788	1.03	0.51-2.07	0.942
At discharge	1.45	0.76-2.78	0.264	1.12	0.56-2.23	0.754
No BNP decrease	1.15	0.75-1.74	0.526	0.96	0.62-1.5	0.866

Factors included in multivariable models are age, African American, history of COPD, edema, SBP, heart rate, sodium, hemoglobin, BUN and hs-cTnI

BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; CI, confidence interval; COPD, chronic obstructive disease; HF, heart failure; HR, hazard ratio; hs-cTnI, high sensitivity cardiac troponin I; SBP; systolic blood pressure

in the RELAX-AHF-2 study, no effect was observed on 180-day cardiovascular mortality or HF readmission, although the beneficial effects of serelaxin on NT-proBNP, troponin and cystatin-C were largely similar to the RELAX-AHF trial.[23] The majority of patients with AHF actually progress slowly to a decompensated state with

Table 3
Time to B-type natriuretic peptide decrease and 1-year outcomes

Composite of mortality or HF hospitalization						
	Univariable			Multivariable		
	HR	95% CI	p-value	adjusted HR	95% CI	p-value
Day 1		reference			reference	
Day 2	1.25	0.81-1.93	0.317	1.05	0.67-1.64	0.842
Day 3	1.46	0.84-2.56	0.181	1.23	0.70-2.17	0.469
At discharge	1.69	0.98-2.93	0.060	1.19	0.67-2.12	0.542
No BNP decrease	1.96	1.38-2.79	< 0.001	1.42	0.98-2.04	0.062
Mortality						
	Univariable			Multivariable		
	HR	95% CI	p-value	adjusted HR	95% CI	p-value
Day 1		reference			reference	
Day 2	1.55	0.73-3.28	0.252	1.17	0.55-2.52	0.683
Day 3	2.39	1.00-5.66	0.049	1.85	0.77-4.43	0.167
At discharge	3.10	1.37-7.02	0.007	1.80	0.77-4.21	0.175
No BNP decrease	3.93	2.16-7.16	< 0.001	2.38	1.29-4.38	0.006
HF hospitalization						
	Univariable			Multivariable		
	HR	95% CI	p-value	adjusted HR	95% CI	p-value
Day 1		reference			reference	
Day 2	1.08	0.65-1.8	0.770	0.99	0.59-1.66	0.956
Day 3	1.10	0.55-2.19	0.788	1.03	0.51-2.07	0.942
At discharge	1.45	0.76-2.78	0.264	1.12	0.56-2.23	0.754
No BNP decrease	1.15	0.75-1.74	0.526	0.96	0.62-1.5	0.866

Factors included in multivariable models are age, African American, history of COPD, edema, SBP, heart rate, sodium, hemoglobin, BUN and hs-cTnI

BNP = B-type natriuretic peptide; BUN = blood urea nitrogen; CI = confidence interval; COPD = chronic obstructive disease; HF = heart failure; HR = hazard ratio; hs-cTnI = high sensitivity cardiac troponin I; SBP; systolic blood pressure

Table 4
Factors associated with BNP decrease at day 1

Variables	OR	95% CI	p-value	Adjusted OR	95% CI	p-value
Age (years)	0.98	0.97-0.99	<0.001	0.99	0.97-1.00	0.077
Non-white	1.52	1.08-2.13	0.019	1.06	0.71-1.61	0.755
Jugular vein distension	0.40	0.25-0.63	<0.001	0.46	0.29-0.75	0.002
Systolic blood pressure (mmHg)	1.01	1.01-1.02	<0.001	1.01	1.00-1.01	0.027
Hemoglobin (g/dl)	1.08	1.01-1.16	0.029	1.02	0.95-1.10	0.615
Blood urea nitrogen (mg/dl)	0.98	0.97-0.99	<0.001	1.00	0.99-1.01	0.635
Creatinine (mg/dl)	0.60	0.44-0.82	0.001	0.80	0.55-1.17	0.253
Serum neutrophil gelatinase-associated lipocalin	0.83	0.72-0.96	0.011	0.98	0.82-1.18	0.848
Galectin 3	0.54	0.41-0.71	<0.001	0.71	0.51-0.98	0.038

Table 5
Factors associated with non-BNP decrease at discharge

Variables	OR	95% CI	p-value	Adjusted OR	95% CI	p-value
Age (years)	1.02	1.01-1.03	<0.001	1.02	1-1.03	0.007
Non-white	0.68	0.51-0.91	0.009	0.90	0.63-1.27	0.538
Jugular vein distension	1.38	1.01-1.88	0.044	0.79	0.56-1.59	0.162
Systolic blood pressure (mmHg)	0.99	0.98-0.99	<0.001	0.99	0.99-1.00	0.001
Sodium (mEq/l)	0.93	0.9-0.96	<0.001	0.95	0.91-0.98	0.002
Blood urea nitrogen (mg/dl)	1.01	1.00-1.02	<0.001	1.00	1.00-1.01	0.225
Brain natriuretic peptide	0.85	0.79-0.93	<0.001	0.80	0.73-0.87	<0.001
Galectin 3	1.68	1.37-2.06	<0.001	1.44	1.14-1.82	0.002

Values of serum neutrophil gelatinase-associated lipocalin, brain natriuretic peptide and galectin 3 were log-2 transformed.

CI = confidence interval; OR = odds ratio

changes building gradually over days or even weeks before admission.[24] Thus, the organ damage from congestion also likely develops gradually and not as an acute event. The earlier timing of decongestion within hours or days may not have as significant an impact on clinical outcomes as much as ensuring adequate decongestion before discharge. Residual congestion at discharge may perpetuate continued organ damage during the longer after-discharge period, which can be more prognostic than the timing of decongestion during hospitalization.[7] Controlling congestion in the longer term is of significant importance, as shown in the device study of diastolic pulmonary artery pressure monitoring.[25] Indeed, the use of serial BNP monitoring and targets for this purpose is another, non-invasive approach to achieve this goal.

Our analysis showed lack of jugular vein distension, higher systolic blood pressure and lower galectin 3 were associated with an increased odds of having BNP $\geq$ 30% decrease at day 1, while older age, lower systolic blood pressure, lower sodium, lower BNP and higher galectin 3 were associated an increased odds of having BNP <30% decrease at discharge. Many of these variables are well known for their prognostic importance in HF. Jugular vein distension and hyponatremia are signs of neurohormonal activation and excess volume and water retention, which may not be adequately controlled by discharge and lead to delayed or no BNP decrease at discharge.[26,27] Patients with higher systolic blood pressure may respond well to the diuretic therapy due to the preserved renal perfusion, be better able to tolerate other medical therapy and thus are more likely to achieve decongestion.[28] Higher galectin 3 levels are associated with inflammation, which has been proposed as an important mechanism of cardiorenal syndrome, and thus may be associated with poor diuretic response.[29] These findings may help clinicians identify which patients will be more resistant to decongestive therapy and need closer monitoring to ensure adequate decongestion is achieved prior to discharge.

This study was a retrospective analysis of the prospective AHF cohort. The result is only hypothesis generating and unmeasured confounding factors may have affected the results. Unfortunately, AKINESIS did not adequately record information to further classify AHF or direct measurements of cardiac pressures. Also, echocardiography findings were recorded only in 62% of the patients and thus were not included in the analysis.

In conclusion, among patients with AHF, earlier decongestion but not the earlier time to diuretics was associated with better biomarker trajectories and clinical outcomes. However, after adjustment for confounding factors, residual congestion at discharge rather than the timing of decongestion was an independent predictor of poor prognosis.

Credit Author Statement

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Declaration of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

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