

Effect of Aggressive Diuresis in Acute Heart Failure with Reduced and Preserved Ejection Fraction

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Abstract

Background: HFrEF and HFpEF had distinct hemodynamic characteristics in the setting of acute heart failure (AHF). The objective of our study is to evaluate the differential response to aggressive diuresis in Heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF).

Methods: Patients in DOSE trial with left ventricular ejection fraction (LVEF) measurement were included (n=300), and classified into HFrEF (n=193) and HFpEF (n=107). Effect of high-dose versus low-dose furosemide strategy was compared separately in HFrEF and HFpEF.

Results: High-dose strategy significantly increased change in creatinine and cystatin C at 72 hours in HFpEF (treatment difference: 0.16; 95% confidence interval [CI]: 0.02-0.30 mg/dl; P=0.03 for creatinine, and treatment difference: 0.26; 95% CI: 0.09-0.43 mg/dl; P=0.003 for cystatin C) but not in HFrEF (treatment difference: -0.05, 95% CI: -0.14-0.03 mg/dl; P=0.24 for creatinine, and treatment difference: -0.06, 95% CI: -0.15-0.02 mg/dl; P=0.15 for cystatin C) (P for interaction<0.01 for both). There were significantly more net fluid loss, weight loss, and congestion-free patients at 72 hours in high-dose group in HFrEF, but not in HFpEF. Compared with low-dose group, high-dose group had a significantly lower risk of composite clinical outcome of death, total hospitalizations and unscheduled visits due to heart failure (hazard ratio [HR]: 0.50, 95% CI: 0.27-0.93; P=0.03) in HFrEF, but a comparable risk (HR: 0.99, 95% CI: 0.48-0.23; P=0.98) in HFpEF.

Conclusions: AHF on the basis of HFrEF and HFpEF responded differently to aggressive diuresis. Future trials should be designed separately for HFrEF and HFpEF.

Background

Heart failure, the end stage of various heart diseases, is a great burden for public health and economy. Over the past decades, treatment of heart failure has been established and prognosis of heart failure has been improved, which, however, is limited to heart failure with reduced ejection fraction (HFrEF). The significance for heart failure with preserved ejection fraction (HFpEF), which accounts for approximately 50% of all heart failure cases, was not recognized until recently¹. Although both HFrEF and HFpEF are in the same "heart failure" category, they have very different characteristics, and more importantly, different response to medical treatments². Outpatient medications that are effective in HFrEF failed to improve the prognosis of HFpEF patients². While it is widely agreed that HFpEF needs a different outpatient therapeutic strategy from that of HFrEF, the differential response to acute heart failure (AHF) treatment has not been fully understood. Previous studies showed that AHF on the basis of chronic HFrEF and HFpEF had distinct hemodynamic characteristics³⁻⁵, which warranted reevaluation of AHF treatment separately in HFrEF and HFpEF.

Adjustment of loop diuretic dose is one of the most common practices in AHF management. While high doses of loop diuretics can contribute to rapid fluid removal, it may have harmful effect, such as worsening of renal function⁶. This concern has been addressed by the Diuretic Optimization Strategies Evaluation (DOSE) trial⁷, which showed no significant association of high-dose furosemide and creatinine change. With this conclusion, several followed AHF trials adopted high-dose loop diuretic as the background therapy^{8,9}. However, it is still unknown whether HFrEF and HFpEF respond differently to high-dose diuretic therapy.

Therefore, the objective of this study was to compare the high-dose with low-dose diuretic strategy separately in HFrEF and HFpEF. Renal function, diuresis, and short-term prognosis were evaluated.

Methods

Study population

The DOSE study was a prospective, randomized, double-blind, controlled trial that was designed to test continuous versus bolus administration of intravenous furosemide and high-dose versus low-dose furosemide therapy in AHF patients⁷. Patients were included if they had at least one symptom (dyspnea, orthopnea, or edema) and one sign (rales, peripheral edema, ascites, or pulmonary vascular congestion on chest radiography) of heart failure. A history of chronic heart failure and usage of oral loop diuretic for more than 1 month were also required. Patients were excluded if they had systolic blood pressure < 90 mmHg or a serum creatinine > 3 mg/dl, or if intravenous vasodilators or inotropic agents other than digoxin were required. There were no exclusion criteria pertaining to ejection fraction. The trial was approved by the ethics committee and an informed consent form was signed by each participant.

The trial used a 2-by-2 factorial design. Totally 308 patients were randomized in a 1:1:1:1 ratio to a low-dose or a high-dose strategy (daily intravenous furosemide dose equal to or 2.5 times their daily oral loop diuretic dose in furosemide equivalents) and to administration by continuous intravenous infusion or intravenous bolus every 12 hours. Physicians can adjust the treatment strategy based on patients' response to therapy at 48 hours. They can maintain the treatment strategy, increase the dose by 50% while remaining blinded, or change to oral diuretic in preparation for discharge.

Heart failure subgroup

Subgroup of heart failure was determined by value of the last left ventricular ejection fraction (LVEF) measurement. Among 308 patients in the trial, 300 of them had available LVEF data and were included in this analysis. LVEF was measured by echocardiography in 287 patients, by radionuclide ventriculogram in 3 patients, by left ventriculogram in 6 patients, by MRI in 2 patients, and by other methods in 2 patients. One hundred and ninety-three patients with a LVEF < 40% were categorized as HFrEF, while the remaining 107 patients with a LVEF \geq 40% were categorized as HFpEF.

The original data of the DOSE trial were obtained from the National Institutes of Heart, Lung, and Blood Institute's Biologic Specimen and Data Repository Information Coordinating Center.

Outcome of interest

This study aimed to evaluate the differential response to high-dose versus low-dose furosemide in HFrEF and HFpEF in terms of renal function, diuresis, and short-term clinical outcome.

For renal function, outcomes included change in creatinine and cystatin C at 72 hours measured by core lab, and development of cardiorenal syndrome (defined as an increase in creatinine of >0.3 mg/dl) within 72 hours. To capture the temporal characteristics, change of creatinine at 24 hours, 48 hours, 72 hours, 96 hours, and 7 days measured by local lab were also evaluated.

For diuresis, outcomes included weight change at 72 hours, net fluid loss at 72 hours, area under curve (AUC) of global and dyspnea Visual Analog Scale (VAS) at 72 hours, change in N-terminal pro-brain natriuretic peptide (NT-proBNP) measured by core lab at 72 hours, freedom from congestion at 72 hours, and worsening or persistent heart failure. Freedom from congestion was defined as jugular venous pressure < 8 cm, no orthopnea, and trace peripheral edema or less. Worsening or persistent heart failure was defined as need for rescue therapy over 72 hours. To capture the temporal characteristics, weight change at 24 hours, 48 hours, and 96 hours, and net fluid loss at 24 hours and 48 hours were also evaluated.

For short-term clinical outcome, we evaluated a composite outcome of death, total (first and recurrent) hospitalizations and unscheduled visits for heart failure. The original DOSE study only assessed the first clinical event and ignored recurrent events. However, the DOSE trial itself was underpowered to test the difference in clinical event, let alone the difference in subgroup analysis. It was shown that when treatment effect was consistent during follow-up (or treatment discontinuation rate was low), recurrent-event methods provided greater power than time-to-first methods¹⁰. Therefore, we decided to use a recurrent-event method.

Statistical analysis

Continuous variables were presented as mean \pm standard deviation or median (25th-75th percentile) and were compared using Student's t test or rank sum test, depending on their normality. Categorical variables were presented as number (percentage) and were compared using chi-squared test or Fisher exact test.

Continuous outcomes were evaluated by linear regression model and binary outcomes were evaluated by logistic regression model. For outcomes that had a relevant baseline value, such as change in creatinine, the baseline value was also adjusted. To evaluate the composite clinical outcome, incidence rates were compared. The effect of furosemide dose was also visualized by Nelson-Aalen cumulative hazard

curves¹¹ and quantified by a marginal risk set model proposed by Wei, Lin, and Weissfeld¹². Mode of furosemide administration was adjusted in above models. Because most of the baseline characteristics were comparable between high-dose and low-dose treatment arms in both heart failure subgroups (except for the modest difference in oxygen saturation in HFpEF) (Additional file 1), no additional variable was adjusted.

To test the interaction between heart failure type and treatment strategy, heart failure type and heart failure type-treatment interaction term were added in above models. There is possibility that the detected heart failure type-treatment interaction was confounded by interaction between other baseline characteristics and treatment. Therefore, sensitivity analyses were performed to adjust for the effect of baseline characteristics that differed significantly between HFrEF and HFpEF. For example, gender proportion differed between HFrEF and HFpEF. In the sensitivity analysis, heart failure type, gender, treatment, heart failure type-gender interaction, heart failure type-treatment interaction, and gender-treatment interaction were all included in the model.

Results were reported with 95% confidence interval (CI). A P value < 0.05 was regarded as statistical significance.

Results

Baseline characteristics

There were totally 300 AHF patients included in the analysis, among which 193 had HFrEF and 107 had HFpEF. The mean LVEF was 23.0% in HFrEF and 55.6% in HFpEF. The two heart failure population had substantial differences in baseline characteristics. HFpEF patients were older, had a higher proportion of female and white race. Interestingly, there was no difference in ischemic etiology. HFpEF patients were more likely to have atrial fibrillation or atrial flutter. Implantable cardioverter-defibrillator, usage of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, beta-blockers, and aldosterone antagonists were more prevalent in HFrEF patients. With higher serum creatinine, urea nitrogen, and cystatin C, HFpEF patients had a worse renal function. Serum N-terminal pro-brain natriuretic peptide (NT-proBNP) level was higher in HFrEF than in HFpEF (Table 1).

Table 1
Baseline characteristics of HFrEF and HFpEF population

	HFrEF (n = 193)	HFpEF (n = 107)	P
Age, y	62.5 ± 13.6	77.0 ± 11.2	< 0.001
Male sex, no.(%)	153 (79.3)	69 (64.5)	0.005
White race, no.(%)	128 (66.3)	91 (85.1)	< 0.001
Dose of oral furosemide equivalent, mg/day	130.6 ± 52.3	132.1 ± 51.4	0.80
Ejection fraction, %	23.0 ± 7.2	55.6 ± 9.1	< 0.001
HF hospitalization in previous year, no./total no. (%)	144/191 (75.4)	74/105 (70.5)	0.84
Ischemic HF, no.(%)	114 (59.1)	60 (56.1)	0.62
Atrial fibrillation or flutter, no.(%)	90 (46.6)	71 (66.4)	0.001
Diabetes, no.(%)	98 (50.8)	56 (52.3)	0.80
ICD, no.(%)	111 (57.5)	6 (5.6)	< 0.001
ACEI or ARB, no.(%)	142 (73.6)	50 (46.7)	< 0.001
Beta blocker, no.(%)	167 (86.5)	82 (76.6)	0.03
Aldosterone antagonist, no.(%)	66 (34.2)	20 (18.7)	0.004
SBP, mmHg	115.7 ± 18.1	124.5 ± 22.0	< 0.001
Heart rate, bpm	80.5 ± 16.6	74.2 ± 13.2	< 0.001
Oxygen saturation, %	96.3 ± 3.1	95.3 ± 2.8	0.01
JVP ≥ 8 cm of water, no./total no. (%)	168/185 (90.8)	93/100 (93.0)	0.53
Orthopnea, no./total no. (%)	171/188 (91.0)	88/98 (89.8)	0.75
Serum sodium, mg/dl	137.7 ± 3.8	139.0 ± 3.4	0.005
BUN, mg/dl	35.6 ± 22.0	40.7 ± 22.9	0.06
Creatinine, mg/dl	1.44 ± 0.50	1.59 ± 0.56	0.02
NT-proBNP, pg/ml	5589 (2636–11342)	3781 (2315–7664)	0.03

	HFrEF (n = 193)	HFpEF (n = 107)	P
Cystatin C, mg/l	1.44 ± 0.53	1.75 ± 0.57	< 0.001
ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; BUN = urea nitrogen; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; ICD = Implantable cardioverter-defibrillator; JVP = jugular venous pressure; NT-proBNP = N-terminal pro-brain natriuretic peptide; SBP = systolic blood pressure			

High-dose versus low-dose strategy and renal function

In HFrEF, there was no significant difference in change in serum creatinine between two strategies (0.07 ± 0.31 mg/dl in the low-dose group and 0.02 ± 0.25 mg/dl in the high-dose group; treatment difference: -0.05 , 95% CI: -0.14 - 0.03 mg/dl; $P = 0.24$) and cystatin C (0.15 ± 0.32 mg/dl in the low-dose group and 0.10 ± 0.19 mg/dl in the high-dose group; treatment difference: -0.06 , 95% CI: -0.15 - 0.02 mg/dl; $P = 0.15$). In HFpEF, high-dose furosemide resulted in a significant increase in creatinine (0.00 ± 0.31 mg/dl in low-dose group and 0.15 ± 0.37 mg/dl in high-dose group; treatment difference: 0.16 , 95% CI: 0.02 - 0.30 mg/dl; $P = 0.03$) and cystatin C (0.04 ± 0.39 mg/dl in low-dose group and 0.25 ± 0.42 mg/dl in high-dose group; treatment difference: 0.26 , 95% CI: 0.09 - 0.43 mg/dl; $P = 0.003$) change at 72 hours. A significant interaction was detected between heart failure type and treatment strategy on change in creatinine (P for interaction = 0.009) and cystatin C (P for interaction < 0.001) (Table 2). In the sensitivity analyses, interaction between heart failure type and high-dose strategy was still significant after adjusting for multiple potential confounders (Table 3). No significant association was found between treatment strategy and development of cardiorenal syndrome within 72 hours in both HFrEF and HFpEF (Table 2). Figure 1 showed the temporal characteristic of treatment difference in creatinine change. In HFrEF, high-dose and low-dose strategy resulted in comparable creatinine change over 7 days. In HFpEF, however, high-dose strategy led to a larger increase in creatinine. The treatment difference increased from 24 hours to 72 hours and was sustained through 7 days.

Table 2
Treatment effect of High Dose vs. Low Dose in HFrEF and HFpEF

	Low Dose	High Dose	Treatment difference [#]	P	P for interaction
Continuous endpoints					
Change in creatinine at 72 h, mg/dl),					
HFrEF	0.07 ± 0.31	0.02 ± 0.25	-0.05 (-0.14-0.03)	0.24	0.009
HFpEF	0.00 ± 0.31	0.15 ± 0.37	0.16 (0.02–0.30)	0.03	
Change in cystatin C at 72 h, mg/l					
HFrEF	0.15 ± 0.32	0.10 ± 0.19	-0.06 (-0.15-0.02)	0.15	< 0.001
HFpEF	0.04 ± 0.39	0.25 ± 0.42	0.26 (0.09–0.43)	0.003	
Net fluid loss at 72 h, ml					
HFrEF	3495 ± 2576	5107 ± 3669	1606 (606–2606)	0.002	0.33
HFpEF	3920 ± 2798	4683 ± 3222	712 (-659-2083)	0.31	
Weight change at 72 h, lb					
HFrEF	-5.79 ± 10.68	-9.17 ± 8.07	-3.30 (-6.09 to -0.52)	0.02	0.45
HFpEF	-6.75 ± 6.93	-8.13 ± 9.26	-1.51 (-4.88-1.85)	0.38	
Change in NT-proBNP at 72 hr, pg/ml					
HFrEF	-1312 ± 4354	-2253 ± 4091	-1013 (-2301-275)	0.12	0.78
HFpEF	-1092 ± 3569	-1373 ± 4151	-771 (-2271-729)	0.31	
AUC of Global VAS at 72 h					
HFrEF	4185 ± 1433	4379 ± 1280	271 (-76-618)	0.13	0.91
* Cardiorenal syndrome was defined as an increase in creatinine of > 0.3 mg/dl within 72 hours					

	Low Dose	High Dose	Treatment difference [#]	P	P for interaction
HFpEF	4086 ± 1449	4424 ± 1586	223 (-297-743)	0.40	
AUC of Dyspnea VAS at 72 h					
HFrEF	4530 ± 1566	4711 ± 1404	211 (-1289-522)	0.22	0.46
HFpEF	4337 ± 1526	4513 ± 1639	410 (-91-911)	0.11	
Binary endpoints					
Freedom from congestion at 72 h, no./total no. (%)					
HFrEF	11/96 (11.5)	21/90 (23.3)	2.36 (1.06–5.24)	0.04	0.43
HFpEF	4/43 (9.3)	7/61 (11.5)	1.32 (0.36–4.91)	0.68	
Worsening or persistent heart failure, no./total no. (%)					
HFrEF	30/98(30.6)	17/90(18.9)	0.53(0.27–1.06)	0.07	0.07
HFpEF	8/43 (18.6)	16/61(26.2)	1.87(0.69–5.04)	0.22	
Cardiorenal syndrome* within 72 h, no./total no. (%)					
HFrEF	13/99(13.1)	17/90(18.9)	1.54(0.70–3.39)	0.28	0.46
HFpEF	6/44 (13.6)	17/61(27.9)	2.62(0.92–7.45)	0.07	
AUC = area under curve; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; NT-proBNP = N-terminal pro-brain natriuretic peptide					
[#] Treatment difference was estimated using the regression coefficient for continuous variables and odd ratios for binary variables					
* Cardiorenal syndrome was defined as an increase in creatinine of > 0.3 mg/dl within 72 hours					

Table 3

Interaction of heart failure type and high-dose strategy in creatinine and cystatin C change at 72 h after adjusting for interaction of potential confounders*

Adjusted variable	P for HF type-treatment interaction	
	Change in creatinine at 72 h	Change in cystatin C at 72 h
Age (\geq or $<$ 50y)	0.02	0.001
Gender	0.02	0.002
White race	0.02	0.001
Atrial fibrillation or flutter	0.005	$<$ 0.001
ICD	0.008	0.001
ACEI or ARB	0.048	0.001
Beta blocker	0.01	$<$ 0.001
Aldosterone antagonist	0.003	$<$ 0.001
SBP (\leq or $>$ 115 mmHg)	0.009	$<$ 0.001
Heart rate (\leq or $>$ 76 bpm)	0.005	0.001
Oxygen saturation (\leq or $>$ 96%)	0.008	0.001
Serum sodium (\leq or $>$ 138 mg/dl)	0.01	0.001
NT-proBNP (\leq or $>$ 4461 pg/ml)	0.008	0.001
GFR (\geq or $<$ 50 ml/min/1.73 m ²)	0.01	$<$ 0.001
* In the model adjusted for interaction of variable X, X itself, X-heart failure type interaction, and X-treatment interaction were added.		
ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; GFR = glomerular filtration rate; HF = heart failure; ICD = Implantable cardioverter-defibrillator; NT-proBNP = N-terminal pro-brain natriuretic peptide; SBP = systolic blood pressure		

High-dose versus low-dose strategy and diuresis

In HFREF, high-dose furosemide therapy significantly increased net fluid loss (3495 ± 2576 ml in low-dose group and 5107 ± 3669 ml in high-dose group; treatment difference: 1606, 95% CI: 606–2606 ml; $P = 0.002$) and weight loss (weight change, -5.79 ± 10.68 lb in low-dose therapy and -9.17 ± 8.07 lb in high-dose group; treatment difference: -3.30, 95% CI: -6.09 to -0.52 lb; $P = 0.02$) at 72 hours. There were also significantly more patients free from congestion at 72 hour in high-dose group (odds ratio [OR]: 2.36, 95%

CI: 1.06–5.24; $P = 0.04$). In HFpEF, although there was numerically more net fluid loss (3920 ± 2798 ml in low-dose group and 4683 ± 3222 ml in high-dose group; treatment difference: 712, 95% CI: -659-2083 ml; $P = 0.31$), weight loss (weight change, -6.75 ± 6.93 lb in low-dose therapy and -8.13 ± 9.26 lb in high-dose group; treatment difference: -1.51, 95% CI: -4.88-1.85 lb; $P = 0.38$), and more patients free from congestion at 72 hours (OR: 1.32, 95% CI: 0.36–4.91; $P = 0.68$) in high-dose group, these differences were not statistically significant. The absolute values of treatment difference of these outcomes were also numerically lower in HFpEF than in HFrEF, but no significant interaction was detected. No significant differences were found between treatment arms in change in NT-proBNP, AUC of global and dyspnea VAS, worsening or persistent heart failure in both heart failure type (Table 2). Figure 2 captured the temporal changes of treatment difference in net fluid loss and weight change. In HFrEF, treatment difference in both net fluid loss and weight loss peaked at 48 hours, while in HFpEF, the absolute treatment difference remained at a low and non-significant level throughout the study period.

High-dose versus low-dose strategy and the short-term clinical outcome

Table 4 showed the numbers of the composite clinical outcome and its components during follow-up. In HFrEF, there were 45 and 24 events in low-dose and high-dose group. In HFpEF, the corresponding numbers were 19 and 24, respectively. The incidence rates of hospitalization due to heart failure ($P = 0.045$) and the composite outcome ($P = 0.01$) was significantly lower in high-dose compared with low-dose group in HFrEF. In HFpEF, there was no significant difference in incidence rates of these events in two treatment arms. In the marginal risk set model, compared with low-dose strategy, high-dose strategy reduced 50% of risk of the composite outcome in HFrEF (Hazard ratio [HR]: 0.50, 95% CI: 0.27–0.93; $P = 0.03$), but did not significantly affect the risk in HFpEF (HR: 0.99, 95% CI: 0.48–2.03; $P = 0.98$). However, no significant interaction was detected (P for interaction = 0.18) (Fig. 3).

Table 4

Difference in incidence rate of the composite outcome and its components in High Dose vs. Low Dose

	Low Dose	High Dose	Difference in incidence rate	P
HFrEF				
Follow-up period, patient-months	148.9	148.2		
Death	11	7	-0.03(-0.08-0.03)	0.36
HF hospitalization	27	14	-0.09(-0.17-0.00)	0.045
Unscheduled visit due to HF	7	3	-0.03(-0.07-0.01)	0.23
Composite outcome*	45	24	-0.14(-0.25 to -0.03)	0.01
HFpEF				
Follow-up period, patient-months	72.8	91.8		
Death	3	8	0.05(-0.03-0.12)	0.28
HF hospitalization	14	12	-0.06(-0.19-0.06)	0.33
Unscheduled visit due to HF	2	4	0.02(-0.04-0.07)	0.63
Composite outcome*	19	24	0.00(-0.16-0.16)	1.00
HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction				
* The composite outcome was composed of death, total hospitalizations or unscheduled visits due to HF				

Discussion

In this study, we found that HFrEF and HFpEF patients responded differently to high-dose vs. low-dose furosemide therapy. In HFrEF, high-dose strategy increased rate of fluid removal and improved short-term prognosis without sacrificing renal function. On the contrary, in HFpEF, high-dose strategy led to deterioration of renal function, but did not significantly facilitate fluid removal or improve prognosis.

Differential response to AHF treatment in HFrEF and HFpEF

Previous studies have already indicated the differential response of HFrEF and HFpEF to AHF treatment. Schwartzberg et al. reported that in response to vasodilation treatment with nitroprusside, HFpEF patients experienced a greater blood pressure decrease, less improvement in cardiac output and stroke volume compared with HFrEF³. A post hoc analysis of the Renal Optimization Strategies trial indicated

HFrEF and HFpEF patients responded differently to dopamine treatment. Dopamine enhanced decongestion and improved outcome in HFrEF, but it did the opposite in HFpEF¹³. Along with our results, these data suggested that HFrEF and HFpEF differed from each other not only in outpatients setting, but also in acute decompensated onset.

Differences of volume status in HFrEF and HFpEF

A possible explanation for the differential response would be difference in volume status. Previous studies showed that HFrEF was more likely to suffer from intravascular volume expansion. In contrast, volume overload in HFpEF appeared more attributable to interstitial instead of intravascular fluid^{4, 5}. Therefore, the circulation system in HFpEF might be more sensitive to intravascular volume reduction than in HFrEF. Indeed, Takei et al. showed that plasma volume reduction was associated with worsening of renal function only in HFpEF but not in HFrEF¹⁴. Due to the difference in intravascular volume, high-dose diuretic therapy was more likely to cause intravascular hypovolemia in HFpEF, which in turn led to deterioration of renal function¹⁵ and diuretic resistance¹⁶. On the contrary, patients with HFrEF were more likely to have intravascular hypervolemia, and therefore, volume reduction by aggressive diuresis could be beneficial because hypovolemia was less likely to develop.

Potential role of hemoconcentration-guided diuresis in HFpEF

Loop diuretic dose adjustment is one of the most important parts in AHF management. Given the sensitivity to intravascular volume change in HFpEF, hemoconcentration-guided diuresis could be an option for these patients^{15, 17}. It was believed that the change in intravenous volume is determined by the balance between diuretic fluid removal and plasma refill from interstitial space. Diuresis at a rate greater than plasma refill resulted in hemoconcentration¹⁵. While hemoconcentration was associated with improved outcome¹⁸, excessive hemoconcentration could lead to deterioration in renal function¹⁵. Timing of hemoconcentration was also of clinical importance. Early hemoconcentration was more likely to be transient, which might be caused by gradual fluid refill from interstitial space. Compared with persistent hemoconcentration, transient hemoconcentration appeared to be more harmful in terms of renal function, but less beneficial in terms of post-discharge prognosis¹⁸. Therefore, the extent and speed of hemoconcentration should be carefully monitored, especially in HFpEF. Fortunately, numerous studies have proved that hemoconcentration could be easily monitored by measurements such as hemoglobin¹⁸⁻²⁰. Therefore, tailoring dose of diuretic according to serial measurements of hemoconcentration could potentially preserve renal function and achieve sustaining decongestion in HFpEF.

Implication for future clinical trials

Given that the difference is now gradually recognized between HFrEF and HFpEF in AHF setting, more trials testing different treatment strategies will be needed for HFpEF. As loop diuretic is still the cornerstone of AHF management, an optimal loop diuretic strategy is needed as the background therapy for these trials. Results of our study suggested that the low-dose strategy (intravenous dose equal to oral dose) is a better candidate than high-dose strategy (intravenous dose 2.5 times oral dose). Results from trials that compared treatments on the basis of high-dose loop diuretic would be hard to interpret⁹.

Limitation

Some limitations had to be taken into consideration in this study. First, there was no limitation for the date of LVEF measurement. LVEF might be measured a long time before randomization in some patients, which would introduce bias in heart failure type classification. Second, the sample size was limited. Although a trend of differential effect was observed between HFrEF and HFpEF in several outcomes, the interaction tests did not yield significant results. Third, the DOSE trial as well as our subgroup analysis was underpowered to test the difference in clinical events. The results about the composite clinical outcome needed to be further validated in a larger dataset.

Conclusion

In conclusion, AHF on the basis of HFrEF and HFpEF responded differently to aggressive loop diuretic therapy. High-dose furosemide enhanced decongestion and improved short-term prognosis in HFrEF, but it worsened the renal function without other significant benefit in HFpEF. Future trials for AHF needed to be designed separately for HFrEF and HFpEF.

List Of Abbreviations

ACEI = angiotensin-converting enzyme inhibitor;

AF = atrial fibrillation;

AHF = acute heart failure;

ARB = angiotensin-receptor blocker;

BUN = urea nitrogen;

AUC = area under curve;

BMI = body mass index;

CHD = coronary heart disease;

CI = confidence interval;

COPD = chronic obstructive pulmonary disease;

CV = cardiovascular;

DOSE trial = Diuretic Optimization Strategies Evaluation trial;

GFR = glomerular filtration rate;

HF = heart failure;

HFpEF = heart failure with preserved ejection fraction;

HFrEF = heart failure with reduced ejection fraction;

HR = hazard ratio;

ICD = implantable cardioverter-defibrillator;

JVP = jugular venous pressure;

LVEF = left ventricular ejection fraction;

NT-proBNP = N-terminal pro-brain natriuretic peptide;

OR = odds ratio;

SBP = systolic blood pressure;

VAS = visual analog scale

Declarations

Ethics approval and consent to participate

The trial was approved by the ethics committee and an informed consent form was signed by each participant.

Consent for publication

Not applicable.

Availability of data and materials

The original data of the DOSE trial were obtained from the National Institutes of Heart, Lung, and Blood Institute's Biologic Specimen and Data Repository Information Coordinating Center. The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable.

Authors' contributions

XH drafted the manuscript. XH and BD designed the subject. BD, RX, JZ and ZW analyzed and interpreted the data. YW, YZ and DW revised the manuscript. YD, JH and CL conceived and supervised this manuscript.

Acknowledgement

Not applicable.

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Figures

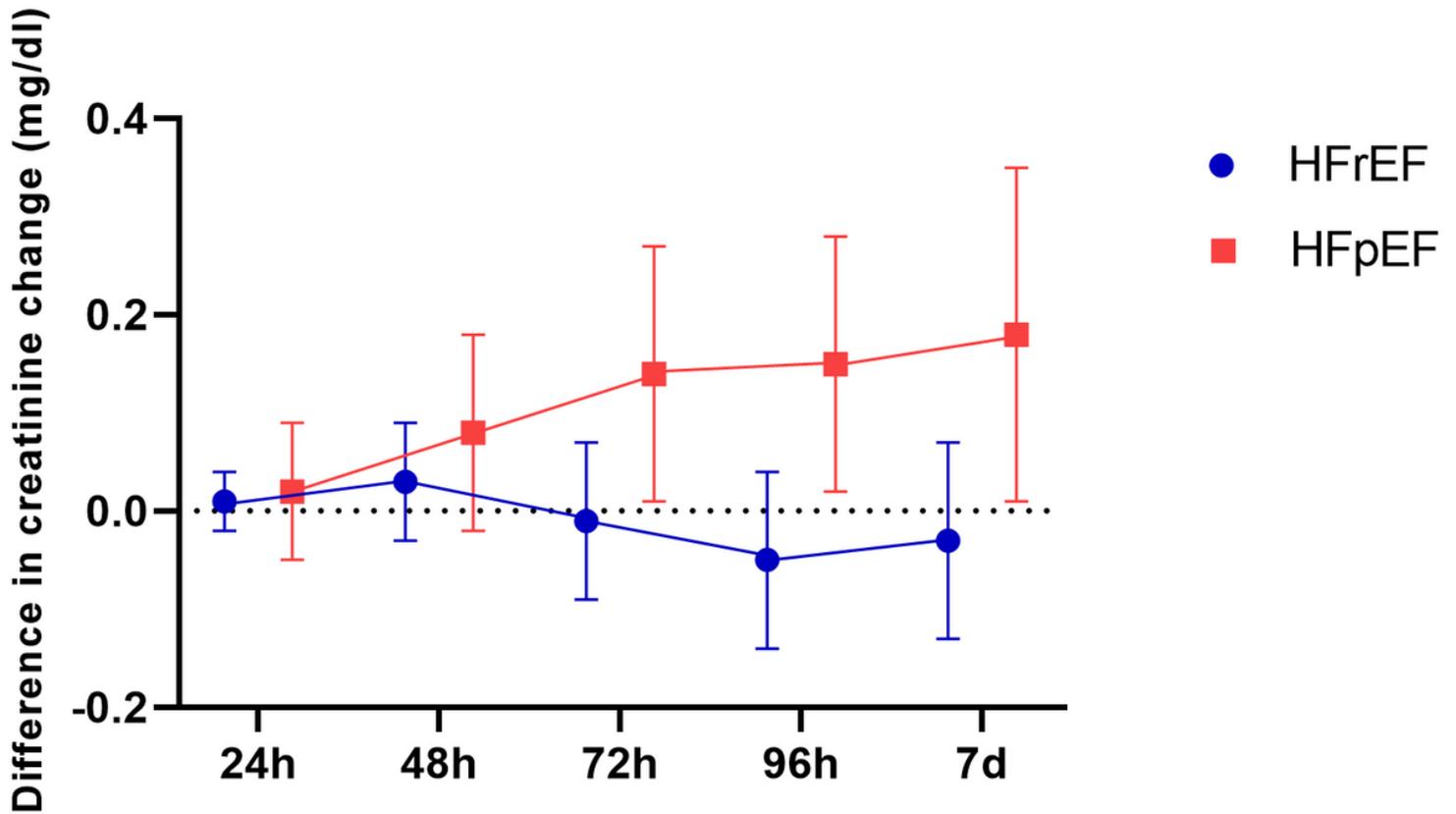


Figure 1

Temporal characteristic of treatment difference of high-dose versus low-dose strategy in creatinine change. Treatment difference was evaluated by linear regression models. In HFrEF, the two treatment arms resulted in comparable creatinine change over 7 days. However, in HFpEF, compared to low-dose strategy, high-dose strategy led to a larger increase in creatinine. HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction.

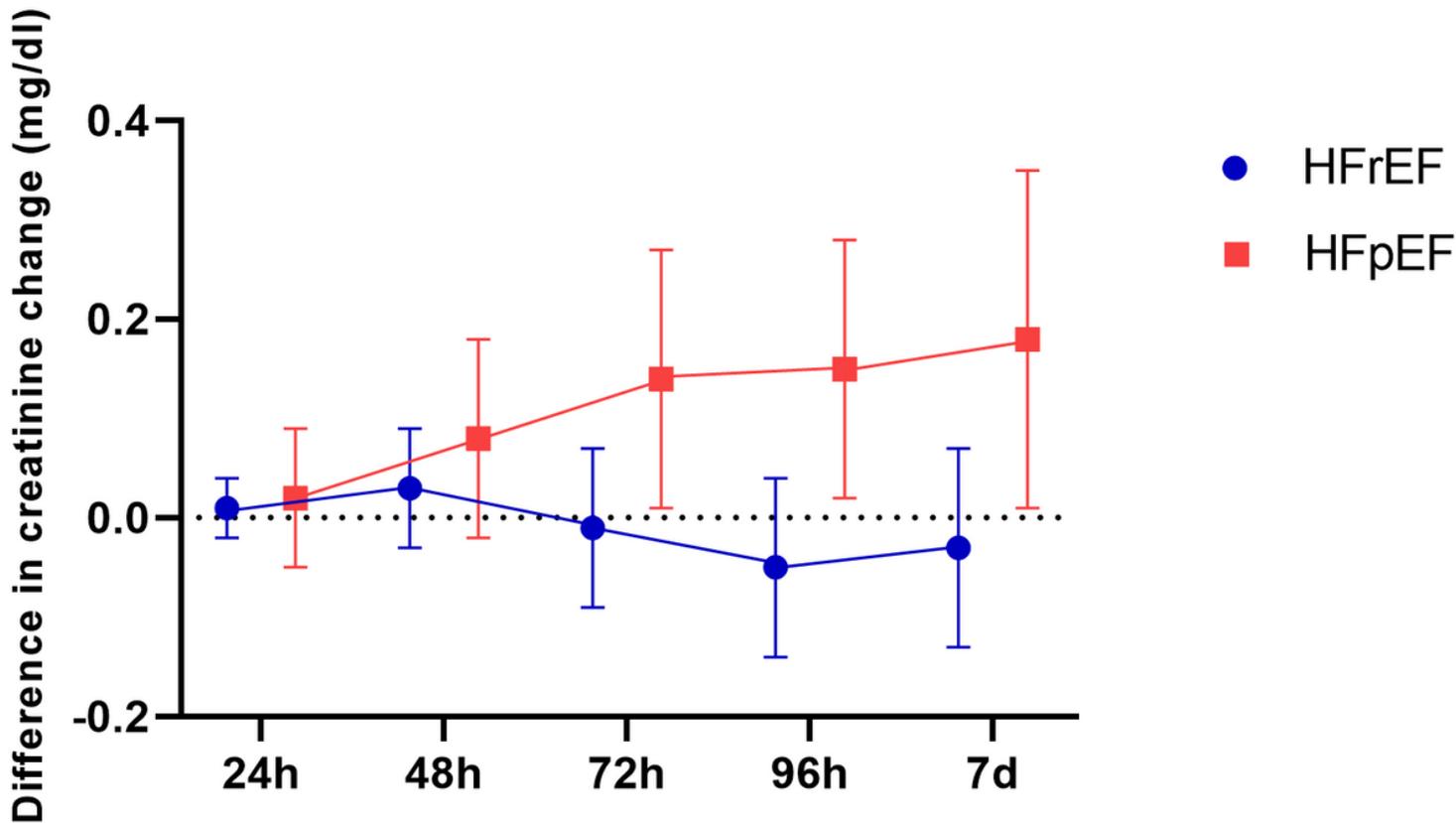


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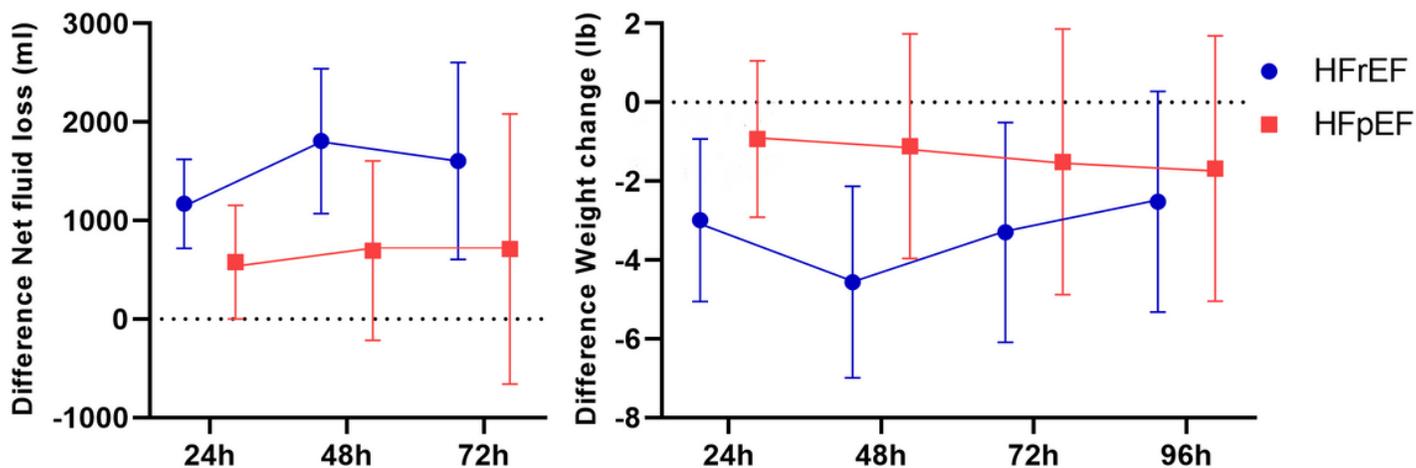


Figure 2

Temporal characteristic of treatment difference of high-dose versus low-dose strategy in net fluid loss and weight change. Treatment difference was evaluated by linear regression models. In HFrEF, differences of change in net fluid loss and weight loss peaked at 48 hours between the two treatment arms, while in HFpEF, treatment difference remained at a non-significant level. HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction.

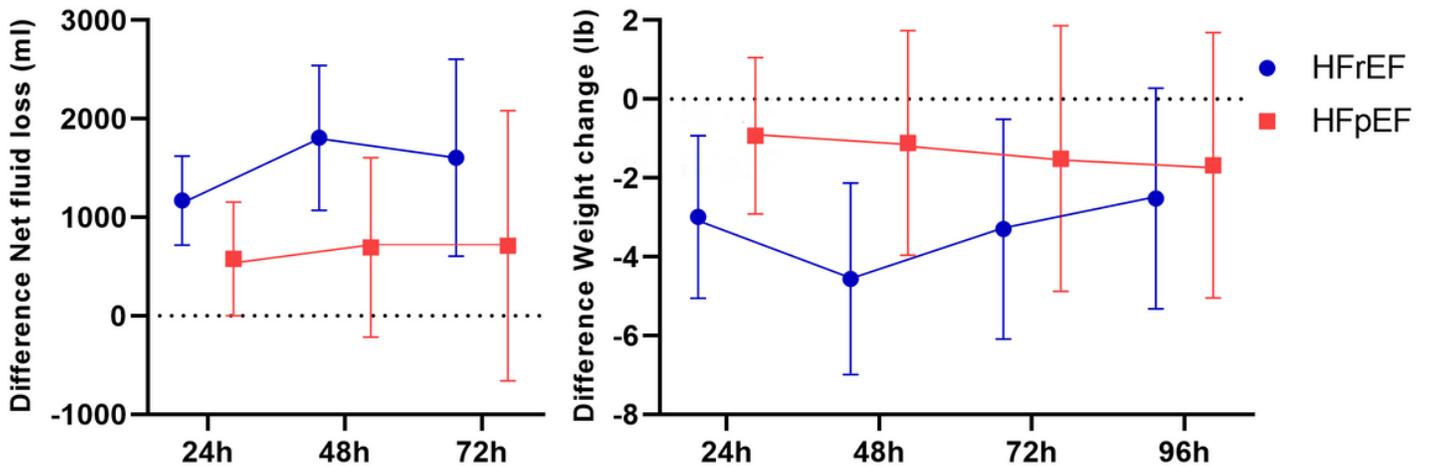
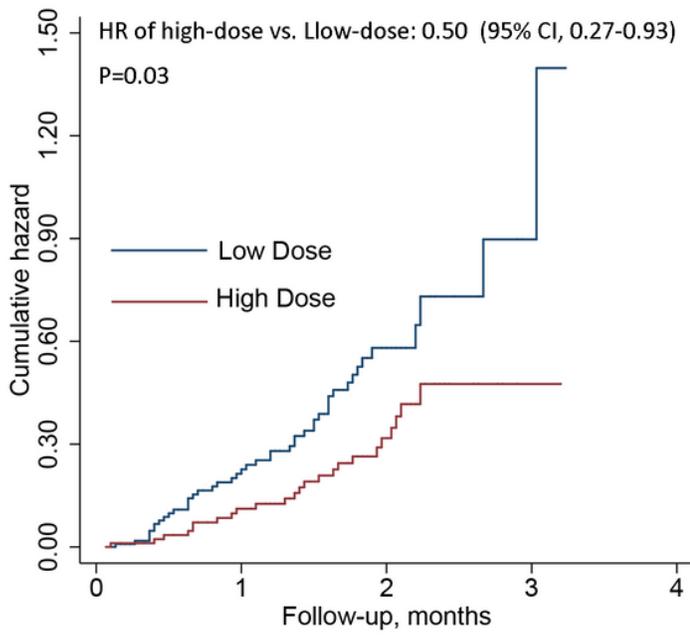


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A HFrEF



B HFpEF

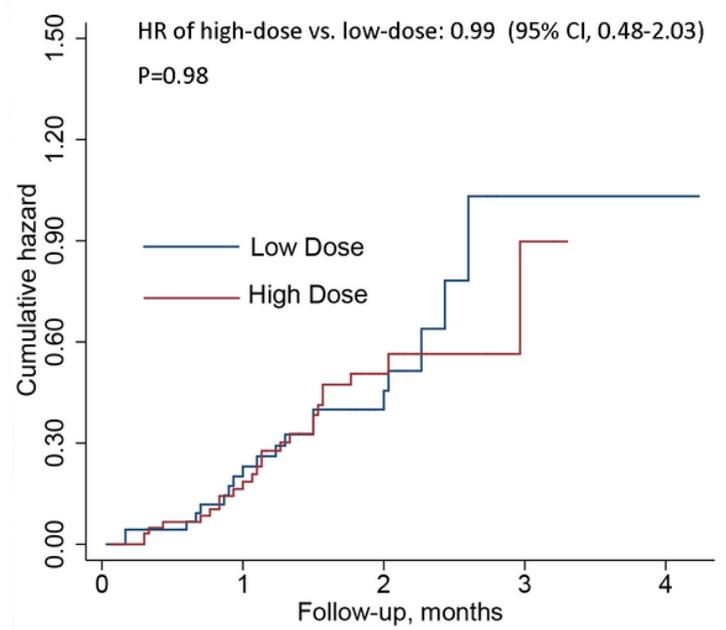
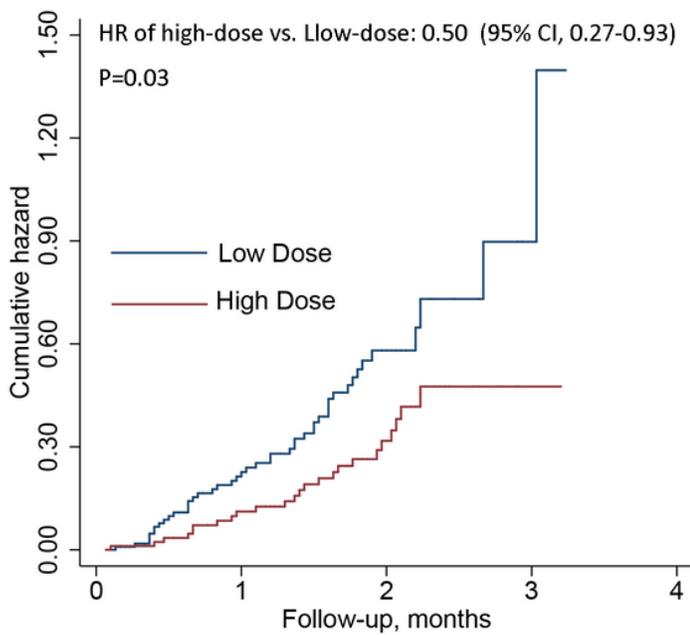


Figure 3

(Graphic Abstract) Nelson-Aalen failure curves for high-dose versus low-dose strategy in (A) HFrEF and (B) HFpEF patients. In the marginal risk set models, high-dose strategy significantly reduced the risk of the composite outcome in HFrEF but not in HFpEF. CI = confidence interval; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction.

A HFrEF



B HFpEF

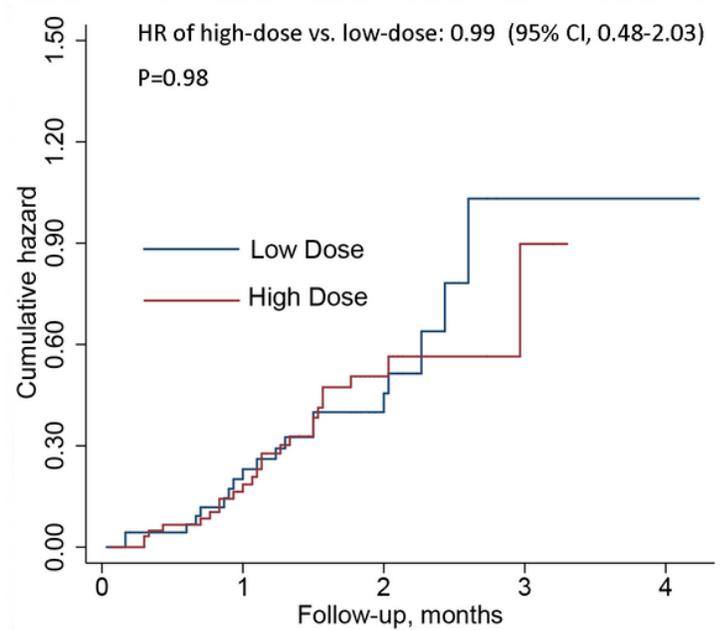


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