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ORIGINAL RESEARCH ARTICLE

Effect of aggressive diuresis in acute heart failure with reduced and preserved ejection fraction

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Abstract

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

Methods and results Patients in the Diuretic Optimization Strategies Evaluation trial with left ventricular ejection fraction measurement were included (n = 300) and classified into HFrEF [left ventricular ejection fraction (LVEF) $<$ 40%] (n = 193) and HFpEF (LVEF $\geq$ 40%) (n = 107). Effect of high-dose vs. low-dose furosemide strategy was compared separately in HFrEF and HFpEF. In HFrEF, high-dose strategy did not increase change in creatinine or cystatin C at 72 h [treatment difference: −0.05, 95% confidence interval (CI): −0.14 to 0.03 mg/dL; P = 0.23 for creatinine, and treatment difference: −0.06, 95% CI: −0.15 to 0.02 mg/dL; P = 0.15 for cystatin C] compared with low-dose strategy, but there were significantly more net fluid loss, weight loss, and congestion-free patients at 72 h in high-dose group. It was also associated with a significantly lower risk of composite clinical outcome of death, total hospitalizations, and unscheduled visits due to heart failure. In HFpEF, high-dose strategy significantly increased change in creatinine and cystatin C at 72 h (treatment difference: 0.16; 95% 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 did not significantly affect net fluid loss, weight loss, proportion of congestion-free patients at 72 h, and risk of the composite clinical outcome.

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

Keywords Acute heart failure; Heart failure with reduced ejection fraction; Heart failure with preserved ejection fraction; Aggressive diuresis; Loop diuretics

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Introduction

Heart failure, the end stage of various heart diseases, is a great burden for public health and economy. The significance of heart failure with preserved ejection fraction (HFpEF), which accounts for approximately 50% of all heart failure cases, was not recognized until recently.[1] Although both heart failure with reduced ejection fraction (HFrEF) and HFpEF are in the same 'heart failure' category, they have very different characteristics, and more importantly, different response to medical treatments.[2] Differential responses of HFrEF and HFpEF to acute heart failure (AHF) treatment have not been fully understood. Previous studies showed that AHF on the basis of chronic HFrEF and HFpEF had distinct haemodynamic characteristics,[3–5] which warranted re-evaluation 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.[6] The Diuretic Optimization Strategies

Evaluation (DOSE) trial[7] was designed to evaluate the efficacy and safety of high-dose vs. low-dose diuretic and administration by bolus vs. continuous infusion. Although high-dose therapy led to a higher risk of cardiorenal syndrome, it was not associated with significantly increased creatinine, which was the primary endpoint of the trial. Thereafter, several 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. Both efficacy and safety endpoints were evaluated.

Methods

Study population

The DOSE study was a prospective, randomized, double-blind, controlled trial that was designed to test continuous vs. bolus administration of intravenous furosemide and high-dose vs. low-dose furosemide therapy in AHF patients.[7] Patients were included if they had at least one symptom (dyspnoea, orthopnoea, or oedema) and one sign (rales, peripheral oedema, 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 two-by-two 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 h. Physicians can adjust the treatment strategy based on patients' response to therapy at 48 h. 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 vs. low-dose furosemide in HFrEF and HFpEF in terms of efficacy and safety endpoints.

Efficacy endpoints included weight change at 72 h, net fluid loss at 72 h, area under curve of global and dyspnoea visual analogue scale at 72 h, change in N-terminal pro-brain natriuretic peptide (NT-proBNP) measured by core lab at 72 h, freedom from congestion at 72 h, and worsening or persistent heart failure. Freedom from congestion was defined as jugular venous pressure $<$ 8 cm, no orthopnoea, and trace peripheral oedema or less. Worsening or persistent heart failure was defined as need for rescue therapy (additional open label loop diuretic, addition of thiazide, intravenous vasoactive agent for heart failure treatment, ultrafiltration, mechanical circulatory, or respiratory support) over 72 h. To capture the temporal characteristics, weight change at 24, 48, and 96 h and net fluid loss at 24 and 48 h were also evaluated. We also exploratory evaluated the short-term prognosis with 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 a 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 methods.[10] Therefore, we decided to use a recurrent-event method.

Safety endpoints included change in creatinine and cystatin C at 72 h measured by core lab, and development of worsening of renal function (defined as an increase in creatinine of $>$0.3 mg/dL within 72 h or an increase in creatinine of $>$0.3 mg/L at 72 h). To capture the temporal characteristics, changes of creatinine at 24, 48, 72, 96 h, and 7 days measured by local lab were also evaluated.

Statistical analysis

Continuous variables were presented as mean ± 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 χ^2 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 curves[11] and quantified by a marginal risk set model proposed by Wei et al.[12] 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) (Supporting Information, *Table S1*), 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. We calculated the statistical power to detect a difference treatment effect in terms of change in cystatin C using the PASS 15 software. Difference in treatment effect between HFrEF and HFpEF was presumed to be 0.30 mg/L, and α was set to 0.05. Other parameters, such as standard deviation of residuals and independent variables, were calculated using the DOSE data set. This study had 93% statistical power to detect the treatment difference change in cystatin C.

Significant differences were found between HFrEF and HFpEF in baseline renal function and age (*Table 1*), which could be important confounders. Therefore, a sensitivity analysis was performed. One-to-one propensity score matching according to baseline glomerular filtration rate and age was performed. Each HFpEF patient was matched to an HFrEF patient with the closest propensity score. The maximum difference in propensity score of a patient pair was set to 0.2 to ensure the overall comparability of HFrEF and HFpEF cohort. Finally, 93 HFrEF patients were matched to 93 HFpEF patients. Analyses with a significant result were repeated in this patients set.

Subgroup analyses stratified by baseline glomerular filtration rate ($\geq$ or $<$50 mL/min/1.73 m^2) and age ($\geq$ or $<$70 years) were also performed.

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 and had a higher

Table 1 Baseline characteristics of HFrEF and HFpEF population

Characteristic	HFrEF (n = 193)	HFpEF (n = 107)	P
Age (years)	62.5 ± 13.6	72.7 ± 11.2	<0.001
Male sex, *n* (%)	153 (79.3)	69 (64.5)	0.005
White race, *n* (%)	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, *n*/*N* (%)	144/191 (75.4)	74/105 (70.5)	0.36
Ischaemic HF, *n* (%)	114 (59.1)	60 (56.1)	0.62
Atrial fibrillation or flutter, *n* (%)	90 (46.6)	71 (66.4)	0.001
Diabetes, *n* (%)	98 (50.8)	56 (52.3)	0.80
ICD, *n* (%)	111 (57.5)	6 (5.6)	<0.001
ACEI or ARB, *n* (%)	142 (73.6)	50 (46.7)	<0.001
Beta blocker, *n* (%)	167 (86.5)	82 (76.6)	0.03
Aldosterone antagonist, *n* (%)	66 (34.2)	20 (18.7)	0.004
SBP (mmHg)	115.7 ± 18.1	124.5 ± 21.7	<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 $\geq$ 8 cm of water, *n*/*N* (%)	168/185 (90.8)	93/100 (93.0)	0.53
Orthopnoea, *n*/*N* (%)	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 (2636–11 342)	3781 (2315–7664)	0.03
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.

proportion of female and white race. Interestingly, there was no difference in ischemic aetiology. 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 NT-proBNP level was higher in HFrEF than in HFpEF (*Table 1*).

High-dose vs. low-dose strategy and safety endpoints

Mean creatinine and cystatin C at baseline and 72 h were summarized in *Table S2*. In HFrEF, there was no significant difference in change in serum creatinine (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 to 0.03 mg/dL; P = 0.23) 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 to 0.02 mg/dL; P = 0.15) between two strategies. In HFpEF, high-dose furosemide resulted in a significant increase in creatinine (0.00 ± 0.31 mg/dL in low-dose group and 0.14 ± 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 h. 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*). High-dose therapy significantly increased the risk of worsening of renal function defined by

Table 2 Treatment effect of high dose vs. low dose in HFrEF and HFpEF

Variable	Low dose	High dose	Treatment difference[a]	*P*	*P* for interaction
Efficacy endpoints					
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 to 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 to 1.85)	0.38	
Change in NT-proBNP at 72 h (pg/mL)					
HFrEF	−1312 ± 4354	−2253 ± 4091	−1013 (−2301 to 275)	0.12	0.78
HFpEF	−1092 ± 3569	−1373 ± 4151	−771 (−2271 to 729)	0.31	
AUC of Global VAS at 72 h					
HFrEF	4185 ± 1433	4379 ± 1280	271 (−76 to 618)	0.13	0.91
HFpEF	4086 ± 1449	4424 ± 1586	223 (−297 to 743)	0.40	
AUC of dyspnoea VAS at 72 h					
HFrEF	4531 ± 1566	4711 ± 1404	212 (−129 to 522)	0.22	0.46
HFpEF	4337 ± 1526	4513 ± 1639	410 (−91 to 911)	0.11	
Freedom from congestion at 72 h, *n*/*N* (%)					
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, *n*/*N* (%)					
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	
Safety endpoints					
Change in creatinine at 72 h (mg/dL)					
HFrEF	0.07 ± 0.31	0.02 ± 0.25	−0.05 (−0.14–0.03)	0.23	0.009
HFpEF	0.00 ± 0.31	0.14 ± 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	
Creatinine increase > 0.3 mg/dL within 72 h, *n*/*N* (%)					
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	
Cystatin C increase > 0.3 mg/L at 72 h, *n*/*N* (%)					
HFrEF	14/80(17.5)	8/72 (11.1)	0.56 (0.22–1.45)	0.23	0.01
HFpEF	6/39 (15.4)	19/52 (36.5)	3.61 (1.23–10.54)	0.02	

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; VAS, visual analogue scale.
[a]Treatment difference was estimated using the regression coefficient for continuous variables and odd ratios for binary variables.

cystatin C change in HFpEF [odds ratio (OR): 3.61, 95% CI: 1.23–10.54; *P* = 0.02], but not in HFrEF (OR: 0.56, 95% CI: 0.22–1.45; *P* = 0.23) (*P* for interaction = 0.01). However, analysis on worsening of renal function defined by creatinine change did not yield any significant result (*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 gradually from 24 to 72 h and was sustained through 7 days.

High-dose vs. low-dose strategy and efficacy endpoints

Mean body weight and median NT-proBNP were summarized in *Table S2*. 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 h (*Table 2*). There were also significantly more patients free from congestion at 72 h in high-dose group (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 to 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 to 1.85 lb; *P* = 0.38), and more patients free from congestion at 72 h (OR: 1.32, 95% CI: 0.36–4.91; *P* = 0.68) in high-dose group, these differences were not statistical 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, area under curve of global and dyspnoea visual analogue scale, 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 h, while in HFpEF, the absolute treatment difference remained at a low and non-significant level throughout the study period.

Table 3 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) were 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

Figure 1 Temporal characteristic of treatment difference of high-dose vs. low-dose strategy in creatinine change. HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

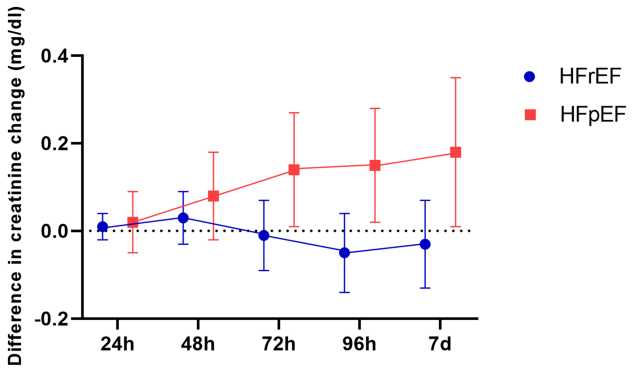
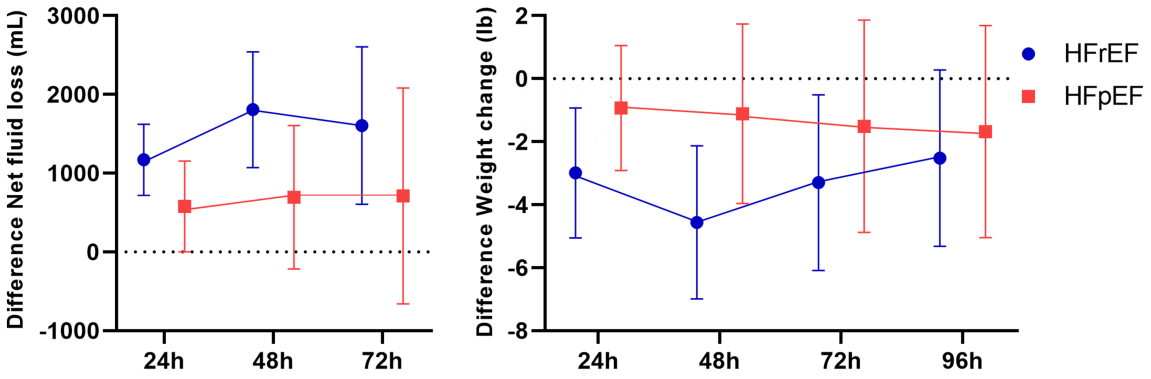


Figure 2 Temporal characteristic of treatment difference of high-dose vs. low-dose strategy in net fluid loss and weight change. HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.



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strategy, high-dose strategy reduced 50% of risk of the composite outcome in HFrEF (hazard ratio: 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) (*Figure 3*).

Subgroup analysis and sensitivity analysis

Results of subgroup analyses were summarized in *Table S3*. In patients with a lower glomerular filtration rate (<50 mL/min/1.73 m^2), high-dose therapy resulted in a larger difference in creatinine or cystatin C change between HFrEF and HFpEF. The differential response was more significant in younger patients (<70 years) in terms of creatinine change, but more significant in older patients (≥70 years) in terms of cystatin C change. The inconsistent results might be due to the lack of concordance between creatinine and cystatin C measurement.[13]

Propensity score matching generated cohorts of 93 patients for HFrEF and HFpEF, respectively. Baseline characteristics of these two cohorts were summarized in *Table S4*. Age and baseline renal function were comparable between HFrEF and HFpEF after propensity score matching. Gender, race, atrial fibrillation or flutter, and serum sodium were also balanced between two heart failure types. Results of the sensitivity analysis in these two matched population were summarized in *Table 4*. Most of the results were consistent with those in the original analysis. Some of the analysis, such as interaction test for creatinine change at 72 h, did not yield statistically significant result, but they showed similar trend with the original analysis. This was probably due to the reduced sample size and statistical power.

Table 3 Difference in incidence rate of the composite outcome and its components in high dose vs. low dose

Variable	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 to 0.03)	0.36
HF hospitalization	27	14	−0.09 (−0.17 to 0.00)	0.045
Unscheduled visit due to HF	7	3	−0.03 (−0.07 to 0.01)	0.23
Composite outcome[a]	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 to 0.12)	0.28
HF hospitalization	14	12	−0.06 (−0.19 to 0.06)	0.33
Unscheduled visit due to HF	2	4	0.02 (−0.04 to 0.07)	0.63
Composite outcome[a]	19	24	0.00 (−0.16 to 0.16)	1.00

HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.
[a]The composite outcome was composed of death, total hospitalizations, or unscheduled visits due to HF.

Figure 3 Nelson–Aalen failure curves for high-dose vs. low-dose strategy in (A) HFrEF and (B) HFpEF patients. HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

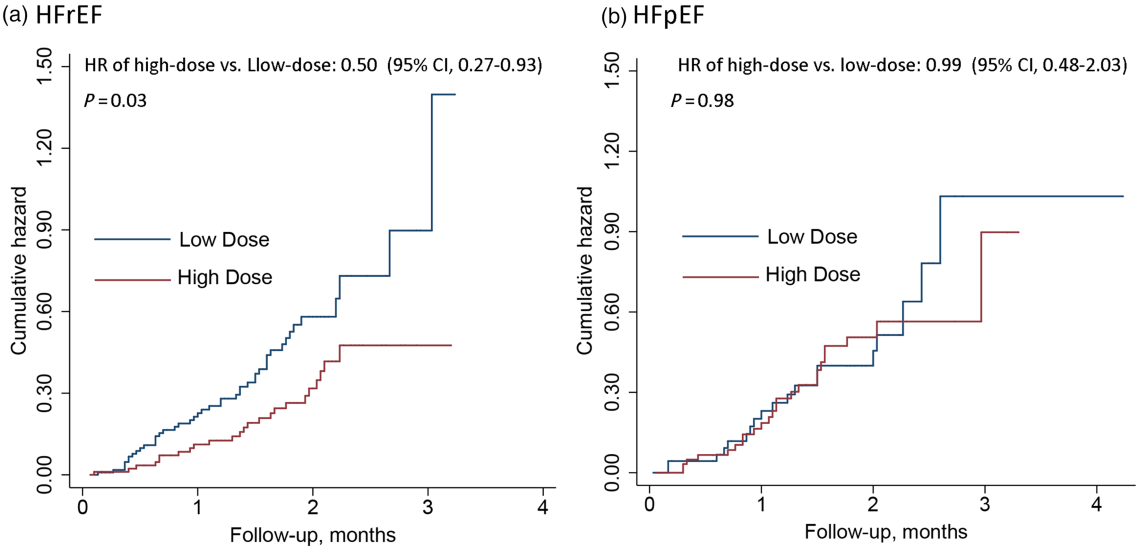

Table 4 Treatment effect of high dose vs. low dose in HFrEF and HFpEF after propensity score matching

Variable	Low dose	High dose	Treatment difference[a]	*P*	*P* for interaction
Efficacy endpoints					
Net fluid loss at 72 h (mL)					
HFrEF	3025 ± 2265	4586 ± 2691	1255 (103–2407)	0.03	0.68
HFpEF	3923 ± 2922	4894 ± 3334	928 (−599 to 2455)	0.23	
Weight change at 72 h (lb)					
HFrEF	−6.66 ± 8.74	−9.31 ± 7.56	−1.81 (−5.38 to 1.76)	0.32	0.78
HFpEF	−7.31 ± 6.98	−8.45 ± 9.90	−1.30 (−5.04 to 2.45)	0.49	
Freedom from congestion at 72 h, *n*/*N* (%)					
HFrEF	4/54 (7.4)	11/35 (31.4)	4.93 (1.39–17.50)	0.01	0.18
HFpEF	4/39 (10.3)	7/52 (13.5)	1.41 (0.38–5.27)	0.61	
Safety endpoints					
Change in creatinine at 72 h (mg/dL)					
HFrEF	−0.02 ± 0.22	−0.03 ± 0.20	0.00 (−0.10 to 0.10)	0.93	0.09
HFpEF	0.00 ± 0.30	0.14 ± 0.36	0.16 (0.01–0.30)	0.03	
Change in cystatin C at 72 h (mg/L)					
HFrEF	0.11 ± 0.29	0.10 ± 0.17	−0.03 (−0.15 to 0.10)	0.68	0.008
HFpEF	0.00 ± 0.35	0.23 ± 0.41	0.27 (0.10–0.43)	0.002	
Cystatin C increase > 0.3 mg/L at 72 h, *n*/*N* (%)					
HFrEF	7/45(15.6)	4/31 (12.9)	0.76 (0.19–3.09)	0.71	0.15
HFpEF	5/36 (13.9)	15/46 (32.6)	3.32 (1.03–10.75)	0.045	

AUC, area under curve; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.
[a]Treatment difference was estimated using the regression coefficient for continuous variables and odd ratios for binary variables.

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 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.

Differential response to AHF treatment in HFrEF and HFpEF

Previous studies have already indicated the differential response of HFrEF and HFpEF to AHF treatment. Schwartzenberg 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 HFrEF.[4] 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 HFpEF.[14] 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 attributable more to interstitial instead of intravascular fluid.[3,5] 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 HFrEF.[15] Because of 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 function[16] and diuretic resistance.[17] 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. Moreover, studies showed that venous pressure was negatively associated with renal perfusion and renal function in heart failure.[18] Aggressive diuresis in HFrEF promoted fluid removal, relieved venous congestion, improved renal perfusion, and thus protected renal function in AHF setting.

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) might be a better candidate than high-dose strategy (intravenous dose 2.5 times oral dose) for HFpEF, because high-dose

strategy caused harm to renal function without providing significant benefit for fluid removal.

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 data set. Fourth, we used an old version of HFpEF definition. The 'HFpEF population' in this study actually covered both HFpEF and heart failure with mid-range ejection fraction according to the latest guideline.[19]

Conclusion

In conclusion, AHF on the basis of HFrEF and HFpEF responded differently to aggressive loop diuretic therapy. High-dose furosemide enhanced decongestion 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.

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Not applicable.

Conflict of interest

Xin He, Bin Dong, Ruicong Xue, Jingjing Zhao, Zexuan Wu, Yuzhong Wu, Yuanyuan Zhou, Dexi Wu, Yugang Dong, Jiangui He, and Chen Liu declare that they have no conflict of interest.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Baseline characteristics of HFrEF and HFpEF population in the 2 treatment arms.
Table S2. Absolute value of outcomes at baseline and 72 hours.
Table S3. Treatment effect of High Dose vs. Low Dose in HFrEF and HFpEF in Subgroup Analysis.
Table S4. Baseline characteristics of HFrEF and HFpEF population after propensity score matching.

References

1. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med* 2006; **355**: 251–259.
2. Sharma K, Kass DA. Heart failure with preserved ejection fraction: mechanisms, clinical features, and therapies. *Circ Res* 2014; **115**: 79–96.
3. Abramov D, Cohen RS, Katz SD, Mancini D, Maurer MS. Comparison of blood volume characteristics in anemic patients with low versus preserved left ventricular ejection fractions. *Am J Cardiol* 2008; **102**: 1069–1072.
4. Schwartzenberg S, Redfield MM, From AM, Sorajja P, Nishimura RA, Borlaug BA. Effects of vasodilation in heart failure with preserved or reduced ejection fraction implications of distinct pathophysiologies on response to therapy. *J Am Coll Cardiol* 2012; **59**: 442–451.
5. Miller WL, Mullan BP. Volume overload profiles in patients with preserved and reduced ejection fraction chronic heart failure: are there differences? A pilot study. *JACC Heart Fail* 2016; **4**: 453–459.
6. Butler J, Forman DE, Abraham WT, Gottlieb SS, Loh E, Massie BM, O'Connor CM, Rich MW, Stevenson LW, Wang Y, Young JB, Krumholz HM. Relationship between heart failure treatment and development of worsening renal function among hospitalized patients. *Am Heart J* 2004; **147**: 331–338.
7. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, LeWinter MM, Deswal A, Rouleau JL, Ofili EO, Anstrom KJ, Hernandez AF, McNulty SE, Velazquez EJ, Kfoury AG, Chen HH, Givertz MM, Semigran MJ, Bart BA, Mascette AM, Braunwald E, O'Connor CM. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med* 2011; **364**: 797–805.
8. Chen HH, Anstrom KJ, Givertz MM, Stevenson LW, Semigran MJ, Goldsmith SR, Bart BA, Bull DA, Stehlik J, LeWinter MM, Konstam MA, Huggins GS, Rouleau JL, O'Meara E, Tang WH, Starling RC, Butler J, Deswal A, Felker GM, O'Connor CM, Bonita RE, Margulies KB, Cappola TP, Ofili EO, Mann DL, Davila-Roman VG, McNulty SE, Borlaug BA, Velazquez EJ, Lee KL, Shah MR, Hernandez AF, Braunwald E, Redfield MM. Low-dose

dopamine or low-dose nesiritide in acute heart failure with renal dysfunction: the ROSE acute heart failure randomized trial. *JAMA* 2013; **310**: 2533–2543.
9. Sharma K, Vaishnav J, Kalathiya R, Hu JR, Miller J, Shah N, Hill T, Sharp M, Tsao A, Alexander KM, Gupta R, Montemayor K, Kovell L, Chasler JE, Lee YJ, Fine DM, Kass DA, Weiss RG, Thiemann DR, Ndumele CE, Schulman SP, Russell SD. Randomized evaluation of heart failure with preserved ejection fraction patients with acute heart failure and dopamine: the ROPA-DOP trial. *JACC Heart Fail* 2018; **6**: 859–870.
10. Claggett B, Pocock S, Wei LJ, Pfeffer MA, McMurray J, Solomon SD. Comparison of time-to-first event and recurrent-event methods in randomized clinical trials. *Circulation* 2018; **138**: 570–577.
11. Aalen OO. Nonparametric inference for a family of counting processes. *Ann Stat* 1978: 701–726.
12. Wei LJ, Lin DY, Weissfeld L. Regression analysis of multivariate incomplete failure time data by modeling marginal distributions. *J Am Stat Assoc* 1989; **84**: 1065–1073.
13. Dupont M, Shrestha K, Singh D, Finucan M, Tang WH. Lack of concordance in defining worsening renal function by rise in creatinine vs rise in cystatin C. *Congest Heart Fail* 2013; **19**: E17–E21.
14. Wan SH, Stevens SR, Borlaug BA, Anstrom KJ, Deswal A, Felker GM, Givertz MM, Bart BA, Tang WH, Redfield MM, Chen HH. Differential response to low-dose dopamine or low-dose nesiritide in acute heart failure with reduced or preserved ejection fraction: results from the ROSE AHF trial (Renal Optimization Strategies Evaluation in Acute Heart Failure). *Circ Heart Fail* 2016; **9**: e002593.
15. Takei M, Kohsaka S, Shiraishi Y, Goda A, Izumi Y, Yagawa M, Mizuno A, Sawano M, Inohara T, Kohno T, Fukuda K, Yoshikawa T. Effect of estimated plasma volume reduction on renal function for acute heart failure differs between patients with preserved and reduced ejection fraction. *Circ Heart Fail* 2015; **8**: 527–532.
16. Boyle A, Sobotka PA. Redefining the therapeutic objective in decompensated heart failure: hemoconcentration as a surrogate for plasma refill rate. *J Card Fail* 2006; **12**: 247–249.
17. Hoorn EJ, Ellison DH. Diuretic resistance. *Am J Kidney Dis* 2017; **69**: 136–142.
18. Sinkeler SJ, Damman K, van Veldhuisen DJ, Hillege H, Navis G. A re-appraisal of volume status and renal function impairment in chronic heart failure: combined effects of pre-renal failure and venous congestion on renal function. *Heart Fail Rev* 2012; **17**: 263–270.
19. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland J, Coats A, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano G, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016; **37**: 2129–2200.