ESC HEART FAILURE
ESC Heart Failure 2022; **9**: 656–666
Published online 11 November 2021 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13696

ORIGINAL ARTICLE

Dose of furosemide before admission predicts diuretic efficiency and long-term prognosis in acute heart failure

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Abstract

Aims The outpatient diuretic dose is a marker of diuretic resistance and prognosis in chronic heart failure (HF). Still, the impact of the preadmission dose on diuretic efficiency (DE) and prognosis in acute HF is not fully known.

Methods and results We conducted an observational and prospective study. All patients admitted for acute HF treated with intravenous diuretic and at least one criterion of congestion on admission were evaluated. Decongestion [physical examination, hemoconcentration, N-terminal pro-brain natriuretic peptide (NT-proBNP) change, and lung ultrasound], DE (weight loss and urine output per unit of 40 mg furosemide), and urinary sodium were monitored on the fifth day of admission. DE was dichotomized into high–low based on the median value. A multivariate Cox regression analysis was conducted to find predictors of HF readmission or mortality. A total of 105 patients were included between July 2017 and July 2019. Mean age was 74.5 ± 12.0 years, 64.8% were male, 33.3% had de novo HF, and mean left ventricular ejection fraction was 46 ± 17%. Median follow-up was 26 [15–35] months. Low DE based on weight loss was associated with a higher previous dose of furosemide (odds ratio [OR] 1.01 [1.00–1.02]), thiazide treatment before admission (OR 9.37 [2.19–40.14]), and lower diastolic blood pressure (OR 0.95 [0.91–0.98]) in the multivariate regression model. Only previous dose of furosemide (OR 1.01 [1.00–1.02]) and haemoglobin at admission (OR 0.76 [0.58–0.99]) were associated with low DE based on urine output in the multivariate analysis. The correlation between the previous dose of furosemide and DE based on weight loss was poor ($r = -0.12$; $P = 0.209$) and with DE based on urine output was weak to moderate ($r = -0.33$; $P < 0.001$). Low DE based on weight loss and urine output was associated with lesser decongestion measured by NT-proBNP ($P = 0.011$; $P = 0.007$), hemoconcentration ($P = 0.006$; $P = 0.044$), and lung ultrasound ($P = 0.034$; $P = 0.029$), but not by physical examination ($P = 0.506$; $P = 0.560$). Survival and event-free survival in acute decompensated HF (ADHF) were lower than in de novo HF; a preadmission dose of furosemide > 80 mg in ADHF identified patients with particularly poor prognosis (log-rank < 0.001). In ADHF, the preadmission dose of furosemide (hazard ratio [HR] 1.34 [1.08–1.67] per 40 mg) and NT-proBNP at admission (HR 1.03 [1.01–1.06] per 1000 pg/mL) were independently associated with mortality or HF readmission in the multivariate Cox regression analysis.

Conclusions The outpatient dose of furosemide before acute HF admission predicts DE and must be taken into account when deciding on the initial diuretic dose. In ADHF, the outpatient dose of furosemide can predict long-term prognosis better than DE during hospitalization.

Keywords Acute heart failure; Diuretic resistance; Prognosis

Received: 18 June 2021; Revised: 21 September 2021; Accepted: 29 October 2021
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Introduction

Acute heart failure (HF) is one of the leading causes of hospitalization worldwide and carries a high risk of mortality and rehospitalization.[1,2] Most of the symptoms related to acute HF are caused by congestion, and loop diuretics represent the mainstay of its treatment.[3] However, not every patient responds well to diuretics; symptoms and signs of congestion may persist even with increasing diuretic dose, which has been called diuretic resistance (DR). Although our understanding of the pathophysiology behind DR is limited, it is thought to result from a complex interplay between cardiac and renal dysfunction, and specific renal adaptation, such as neurohormonal activation and nephron remodelling.[4–6] Moreover, there is no standardized and generally accepted definition of DR, although poor diuretic efficiency (DE) has been associated with increased mortality and HF readmission.[7–11] These studies have defined DE as weight loss, net fluid loss, or urine output per 40 mg of furosemide or equivalent. It appears, however, that the correlation between weight and net fluid loss is modest and that the latter systematically overestimates weight loss.[12] Additionally, these measures can be complex in daily clinical practice and require several days from admission. In chronic HF, a high diuretic dose is a marker of DR and adverse outcomes.[13–16] Nevertheless, the impact of the outpatient dose before admission on DE in acute HF is not fully known.

The study aimed to investigate the predictors of low DE in acute HF, focusing on the diuretic dose before admission and the association between the different DR criteria and the long-term prognosis.

Methods

The design of the 'REsistance to DIuretic in Heart Failure [REDIHF] registry' was described in a previous report.[17] It is an observational and prospective study, which analyses different aspects of DR in patients admitted for HF. All patients admitted for acute HF in the Cardiology Department of the Hospital del Mar (between July 2017 and April 2018) and Hospital Universitario 12 de Octubre (from May 2018 to July 2019) were screened for eligibility. The inclusion criteria were age $>$ 18 years, an N-terminal pro-brain natriuretic peptide (NT-proBNP) $>$ 600 or $>$1000 pg/mL in atrial fibrillation, the need for intravenous diuretic treatment, and at least one criterion of congestion on admission (jugular ingurgitation, lung crackles, ascites, oedema of the lower limbs, or pleural effusion on chest X-ray or lung ultrasound). Patients on renal replacement therapy, under intravenous diuretic treatment for $>$72 h before the screening, admitted to the intensive care unit, and those unable to understand and sign the informed consent were excluded. One physician of the investigation team reviewed the patients admitted to the Cardiology Department every day except on weekends and offered to participate to those who met the inclusion criteria. Every patient gave written informed consent. The study was approved by the hospital's ethics committees and complied with the Declaration of Helsinki and the Declaration of Istanbul.

Past medical history, previous medical treatment, physical examination, blood test with NT-proBNP, and electrocardiography and echocardiography data were collected at admission. The diuretic dose and the rest of the medical treatment were left to the discretion of treating physicians. On the fifth day of admission, we evaluated decongestion by physical examination, hemoconcentration, change in NT-proBNP, and lung ultrasound with a pocket device (VScan, GE Healthcare, Boston, MA, USA). Decongestion was defined by physical examination as the absence of jugular ingurgitation, lung crackles, ascites, and oedema of the lower limbs. Hemoconcentration was assessed as the increase of the haemoglobin level. A decrease of $>$30% of NT-proBNP level was considered decongestion. Lastly, decongestion was defined as the lack of pleural effusion or B-lines in the 28 spaces assessed by lung ultrasound.

Furthermore, on the fifth day, we assessed DE with the weight loss or urine output from admission per unit of 40 mg furosemide or equivalent and visual analogue scale of dyspnoea (0–10) and urinary sodium. The latter was measured before the morning bolus of furosemide. Worsening renal function was defined as an increase in serum creatinine $\geq$ 0.3 mg/dL during hospitalization. An on-site visit with blood and urine tests was made 2 months after enrolment. Subsequent follow-up was left to the discretion of the treating physician. Finally, medical reports were reviewed in all patients at the end of September 2020.

Statistical analysis

Discrete variables were expressed as a proportion, and continuous variables as a mean ± standard deviation or median [interquartile range]. Comparisons were made using the χ^2 test or exact Fisher's test for discrete variables and Student's *t*-test or Mann–Whitney *U* test for continuous variables.

Patients were divided into three different groups depending on the preadmission dose of furosemide: de novo HF, acute decompensated heart failure (ADHF) with a previous daily dose of furosemide $\leq$ 80 mg, and ADHF with a previous daily dose of furosemide $>$ 80 mg (this dose was associated with poor outcomes in chronic HF in previous studies). Baseline characteristics in both ADHF groups were compared with the de novo HF patients.

Diuretic efficiency based on weight loss and urine output was dichotomized into high vs. low based on the median value. The association between low DE and clinical characteristics at admission was assessed with a multivariate logistic

regression analysis. Variables with a univariate association with low DE with a *P*-value of <0.1 were included in the initial model. Variables were removed from the initial model with the stepwise backward method with a cut-off point of $P < 0.05$.

Differences on the fifth day between high vs. low DE in diuretic doses, decongestion variables, urinary sodium, and visual analogue scale of dyspnoea were analysed using the χ^2 test or exact Fisher's test for discrete variables, and Student's *t*-test or Mann–Whitney *U* test for continuous variables.

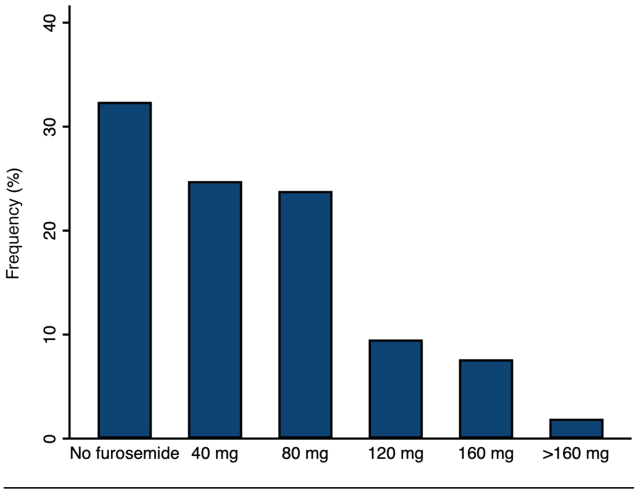
Correlations between the previous dose of furosemide and both DE variables were evaluated using Spearman's rho. Receiver-operating characteristic (ROC) curve analysis was used to assess the area under the ROC curve (AUC) of the dose of furosemide before admission to predict low DE.

Regarding the prognosis, we compared patients with de novo HF, ADHF with the previous dose of furosemide ≤ 80 mg, and ADHF with the previous dose of furosemide > 80 mg. Survival and event-free (death or HF readmission) survival were compared using the Kaplan–Meier curves and the log-rank test. Event-free (death or readmission) survival was also compared between high vs. low DE based on weight loss and urine output and between urinary sodium < 50 vs. ≥ 50 mEq/L. A multivariate Cox regression analysis, including all the variables with $P < 0.1$ in the univariate analysis, was performed to identify independent predictors of event-free (death or HF readmission) survival. Variables were removed from the model with the stepwise backward method with a cut-off point of $P < 0.05$. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for each risk factor. A *P*-value < 0.05 was considered significant. The statistical analysis was performed using Stata software (V.14.0, Stata Corporation).

Results

A total of 105 patients were included between July 2017 and July 2019. Mean age was 74.5 ± 12.0 years, 64.8% were male, 33.3% had de novo HF, mean left ventricular ejection fraction (LVEF) was 46 ± 17%, and median dose of furosemide before admission was 40 [0–80] mg (*Figure 1*). All baseline characteristics are shown in *Table 1*. The median total intravenous dose of furosemide or equivalent received until the fifth day was 300 [203–415] mg. In addition, median weight loss per unit of furosemide was 0.29 [0.12–0.58] kg and median urine output per unit of furosemide was 0.78 [0.48–1.37] L. Mean hospital length of stay was 9.1 ± 5.8 days. Median follow-up, which finished at the end of September 2020, was 26 [15–35] months. Two patients died during hospitalization and 33 in the subsequent follow-up. Moreover, 42 patients were readmitted for HF.

Figure 1 Outpatient daily dose of furosemide before admission.



Determinants of low diuretic efficiency

On one side, low DE based on weight loss was associated with a higher previous dose of furosemide, thiazide treatment before admission, and lower diastolic blood pressure in the univariate and multivariate analysis. On the other side, low DE based on urine output was associated with previous HF diagnosis, moderate-to-severe valvular heart disease, a higher previous dose of furosemide, lower systolic and diastolic blood pressure, lower haemoglobin, and lower glomerular filtration rate in the univariate analyses. Nevertheless, only previous dose of furosemide and haemoglobin at admission were associated with low DE based on urine output in the multivariate regression model. It should be noted that the treatment with mineralocorticoid receptor antagonists before admission was not associated with low DE based on weight loss or urine output (*Table 2*).

Decongestion and low diuretic efficiency

Concerning DE and its effect on decongestion, low DE led to a lesser decongestion. Patients with low DE required a higher dose of furosemide, and continuous diuretic infusion was more frequent. However, both low weight loss and urine output per unit of furosemide were associated with lesser decongestion measured by NT-proBNP, hemoconcentration, and lung ultrasound. Surprisingly, residual congestion measured by physical examination was similar between high vs. low DE. In addition, patients with low DE based on weight loss had more dyspnoea measured by the visual analogue scale and lower urinary sodium, and those with lower DE based on urine output had longer hospital length of stay (*Table 3*).

Table 1 Baseline characteristics

	De novo HF (n = 35)	ADHF–dose of furosemide ≤ 80 mg (n = 50)	P	ADHF–dose of furosemide > 80 mg (n = 20)	P
Age (years)	74 ± 13	75 ± 10	0.767	74 ± 14	0.951
Male sex	26 (74.3%)	31 (62.0%)	0.236	11 (55.0%)	0.143
Diabetes mellitus	11 (31.4%)	25 (50.0%)	0.088	9 (45.0%)	0.314
Arterial hypertension	27 (77.1%)	46 (92.0%)	0.064	17 (85.0%)	0.483
Dyslipidaemia	21 (60.0%)	37 (74.0%)	0.172	12 (60.0%)	1.000
Body mass index (kg/m^2)	28.6 ± 5.1	28.9 ± 5.7	0.825	29.4 ± 4.8	0.601
Chronic kidney disease	8 (22.9%)	19 (38%)	0.140	14 (70%)	0.001
Chronic obstructive pulmonary disease	9 (25.7%)	10 (20.0%)	0.534	6 (30.0%)	0.731
Cerebrovascular disease	3 (8.6%)	5 (10.0%)	1.000	1 (5.0%)	1.000
Peripheral vascular disease	3 (8.6%)	3 (6.0%)	0.687	1 (5.0%)	1.000
Significant coronary artery disease[a]	8 (22.9%)	22 (44.0%)	0.045	6 (30.0%)	0.559
Moderate-to-severe valvular heart disease	7 (20.0%)	24 (48.0%)	0.008	12 (60.0%)	0.003
Atrial fibrillation	19 (54.3%)	30 (60.0%)	0.600	16 (80.0%)	0.082
LVEF (%)	46 ± 15	43 ± 18	0.320	51 ± 18	0.295
HFrEF	11 (31.4%)	24 (48.8%)	0.127	5 (25.0%)	0.614
HFmrEF	6 (17.7%)	4 (8.0%)	0.305	1 (5.0%)	0.402
HFpEF	18 (51.4%)	22 (44.0%)	0.499	14 (70.0%)	0.179
Dose of furosemide before admission (mg)	0 [0–20]	40 [40–80]	<0.001	120 [120–160]	<0.001
Beta-blocker before admission	16 (45.7%)	43 (86.0%)	<0.001	18 (90.0%)	0.001
ACE inhibitor or ARB before admission	23 (65.7%)	27 (54.0%)	0.280	9 (45.0%)	0.134
Sacubitril/valsartan before admission	0 (0%)	6 (12%)	0.040	2 (10.0%)	0.128
MRA before admission	5 (14.3%)	14 (28.0%)	0.135	8 (40.0%)	0.031
SGLT2 inhibitor before admission	1 (2.9%)	1 (2.0%)	1.000	0 (0%)	1.000
NSAIDs before admission	1 (2.9%)	0 (0%)	0.417	0 (0%)	1.000
Haemoglobin at admission (g/dL)	12.7 ± 2.1	12.9 ± 1.9	0.583	11.8 ± 2.1	0.115
Sodium at admission (mmol/L)	141 ± 3	140 ± 4	0.267	140 ± 5	0.648
Glomerular filtration rate at admission (mL/min/1.73 m^2)	62 ± 21	55 ± 21	0.111	44 ± 19	0.002
GGT at admission (U/L)	72 ± 66	80 ± 75	0.651	77 ± 55	0.873
Bilirubin at admission (mg/dL)	0.8 ± 0.5	1.0 ± 0.7	0.102	1.1 ± 1.0	0.234
Albumin at admission (g/dL)	3.9 ± 0.4	3.9 ± 0.5	0.879	3.9 ± 0.5	0.829
NT-proBNP at admission (pg/mL)	3665 [2300–5801]	6000 [2667–12 091]	0.046	5605 [2328–14 540]	0.105

ACE, angiotensin-converting enzyme; ADHF, acute decompensated heart failure; ARB, angiotensin II receptor blocker; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NSAIDs, non-steroidal anti-inflammatory drugs; NT-proBNP, N-terminal pro-brain natriuretic peptide; SGLT2, sodium-glucose contransporter-2.
Differences in baseline characteristics between groups: de novo HF, ADHF with previous daily dose of furosemide ≤ 80 mg, and ADHF with previous daily dose of furosemide > 80 mg. Each group of ADHF was compared with the de novo HF group.
[a]Significant coronary artery disease was defined by invasive coronary angiography as >50% stenosis of the left main stem or >70% stenosis in a major coronary vessel.

Dose of furosemide before admission and diuretic efficiency

As mentioned above, patients with low DE had a higher dose of furosemide before admission. The correlation between the previous dose of furosemide and DE based on weight loss was poor (r = −0.12; P = 0.209) and with DE based on urine output was weak to moderate (r = −0.33; P < 0.001). There was a moderate correlation between DE based on weight loss and DE based on urine output (r = 0.54; P < 0.001) (Supporting Information, *Figure S1*). In addition, the previous dose of furosemide showed an AUC = 0.65 to predict low DE based on weight loss and an AUC = 0.72 to predict low DE based on urine output (Supporting Information, *Figure S2*). A previous daily dose of ≥80 mg was the best cut-off point; it had a positive predictive value of 69.2% and negative predictive value of 62.9% for low DE based on weight loss, and 76.3% and 65.6%, respectively, based on urine output.

Diuretic resistance and long-term outcomes

Survival and event-free (death or HF readmission) survival in ADHF were lower than in de novo HF; besides, a previous daily dose of furosemide > 80 mg in ADHF identified patients with particularly poor prognosis (log-rank < 0.001) (*Figure 2*). Low DE based on urine output was also associated with a worse prognosis (log-rank = 0.009). Still, the difference between high vs. low DE based on weight loss was not statistically significant (log-rank = 0.093) (*Figure 3*). Neither was the difference between high vs. low urinary sodium (log-rank = 0.327).

Table 2 Predictors of low diuretic efficiency

	Low diuretic efficiency based on weight loss		Low diuretic efficiency based on urine output	
	Univariate OR (95% CI)/*P*-value	Multivariate OR (95% CI)/*P*-value	Univariate OR (95% CI)/*P*-value	Multivariate OR (95% CI)/*P*-value
Age (years)	1.00 (0.97–1.03)/0.983		1.01 (0.98–1.05)/0.335	
Male sex	0.82 (0.36–1.84)/0.625		0.55 (0.24–1.28)/0.164	
Arterial hypertension	2.81 (0.82–9.63)/0.101		0.88 (0.29–2.63)/0.812	
Diabetes mellitus	1.04 (0.47–2.28)/0.933		0.82 (0.37–1.81)/0.621	
Dyslipidaemia	1.84 (0.79–4.28)/0.159		0.94 (0.41–2.17)/0.887	
De novo heart failure	0.72 (0.32–1.66)/0.441		0.25 (0.10–0.62)/0.003	NS
Significant coronary artery disease[a]	0.94 (0.42–2.14)/0.891		1.67 (0.72–3.86)/0.233	
Moderate-to-severe valvular heart disease	1.04 (0.47–2.28)/0.933		2.71(1.18–6.22)/0.019	NS
Atrial fibrillation	0.97 (0.43–2.17)/0.938		1.59 (0.70–3.62)/0.266	
LVEF (%)	1.02 (1.00–1.05)/0.070	NS	1.02 (0.99–1.04)/0.207	
Dose of furosemide before admission (mg)	1.01 (1.00–1.02)/0.008	1.01 (1.00–1.02)/0.021	1.02 (1.01–1.03)/0.001	1.01 (1.00–1.02)/0.005
Thiazide before admission	3.68 (1.21–11.19)/0.022	9.37 (2.19–40.14)/0.003	0.47 (0.17–1.27)/0.137	
Beta-blocker before admission	0.97 (0.40–2.37)/0.953		0.92 (0.37–2.29)/0.863	
ACE inhibitor or ARB before admission	1.87 (0.84–4.16)/0.127		0.48 (0.21–1.10)/0.082	NS
Sacubitril/valsartan before admission	0.15 (0.02–1.32)/0.088	NS	0.37 (0.07–1.99)/0.245	
MRA before admission	1.14 (0.47–2.75)/0.776		1.07 (0.44–2.61)/0.870	
Systolic blood pressure at admission (mmHg)	0.98 (0.96–1.00)/0.107		0.98 (0.96–0.99)/0.02	NS
Diastolic blood pressure at admission (mmHg)	0.95 (.092–0.98)/0.003	0.95 (0.91–0.98)/0.002	0.98 (0.96–1.00)/0.02	NS
Heart rate at admission (b.p.m.)	1.00 (0.98–1.02)/0.855		1.00 (0.98–1.02)/0.825	
Haemoglobin at admission (g/dL)	0.91 (0.75–1.11)/0.373		0.71 (0.57–0.90)/0.004	0.76 (0.58–0.99)/0.038
Sodium at admission (mmol/L)	0.95 (0.86–1.05)/0.279		0.96 (0.87–1.06)/0.425	
Glomerular filtration rate at admission (mL/min/1.73 m^2)	0.99 (0.97–1.01)/0.410		0.98 (0.96–1.00)/0.022	NS
Creatinine at admission (mg/dL)	1.39 (0.71–2.72)/0.340		1.80 (0.86–3.78)/0.121	
Urea at admission (mg/dL)	1.00 (0.98–1.02)/0.837		1.02 (0.99–1.04)/0.153	
Albumin at admission (g/dL)	1.00 (0.96–1.05)/0.871		1.00 (0.96–1.05)/0.891	
GGT at admission (U/L)	1.00 (0.99–1.01)/0.972		1.00 (0.99–1.00)/0.591	
Bilirubin at admission (mg/dL)	1.09 (0.63–1.90)/0.752		1.30 (0.74–2.28)/0.368	
NT-proBNP at admission (pg/mL)	1.00 (0.99–1.01)/0.646		0.99 (0.98–1.01)/0.371	

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CI, confidence interval; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NS, not significant; NT-proBNP, N-terminal pro-brain natriuretic peptide; OR, odds ratio.
Association between clinical characteristics at admission and low diuretic efficiency based on weight loss and based on urine output.
[a]Significant coronary artery disease was defined by invasive coronary angiography as >50% stenosis of the left main coronary artery or >70% stenosis in a major coronary vessel.

Table 3 Differences during hospitalization between patients with low vs. high diuretic efficiency

	Diuretic efficiency based on weight loss			Diuretic efficiency based on urine output		
	Low diuretic efficiency	High diuretic efficiency	*P*-value	Low diuretic efficiency	High diuretic efficiency	*P*-value
No congestion on physical examination on the 5th day	45.8%	39.2%	0.506	40.0%	45.8%	0.560
Decrease in NT-proBNP > 30%	48.9%	74.0%	0.011	48.9%	75.5%	0.007
Change in haemoglobin on the 5th day (g/dL)	−0.18 ± 1.19	0.43 ± 0.93	0.006	−0.08 ± 1.15	0.38 ± 1.05	0.044
Increase in haemoglobin on the 5th day	44.9%	70.0%	0.012	54.2%	63.3%	0.363
Lack of B-lines in lung ultrasound on the 5th day	26.8%	48.9%	0.034	25.0%	47.8%	0.029
UNa on the 5th day (mEq/L)	51 ± 30	67 ± 33	0.019	60 ± 33	60 ± 35	0.982
UNa on the 5th day <50 mEq/L	50.0%	34.8%	0.154	40.5%	44.2%	0.729
VAS of dyspnoea on the 5th day (0–10)	2.6 ± 2.6	1.6 ± 2.0	0.035	2.2 ± 2.4	1.5 ± 2.1	0.154
Cumulative dose of furosemide on the 5th day (mg)	330 [220–480]	240 [200–340]	0.029	400 [320–540]	220 [170–260]	<0.001
Dose of furosemide in the 1st day (mg)	100 [60–145]	80 [60–120]	0.272	120 [80–160]	80 [60–80]	<0.001
Dose of furosemide in the 2nd day (mg)	80 [60–160]	60 [60–120]	0.025	120 [80–160]	60 [40–70]	<0.001
Dose of furosemide in the 3rd day (mg)	80 [40–120]	60 [40–80]	0.006	80 [55–120]	40 [40–60]	<0.001
Dose of furosemide in the 4th day (mg)	40 [28–83]	40 [20–60]	0.446	60 [40–120]	40 [0–60]	<0.001
Peak intravenous furosemide dose in 24 h (mg)	120 [80–160]	80 [60–140]	0.065	155 [100–180]	80 [60–95]	<0.001
Intravenous furosemide during >48 h	72.0%	72.5%	0.951	84.0%	59.2%	0.006
Continuous diuretic infusion	20.0%	5.9%	0.041	30.0%	0.0%	<0.001
Cumulative dose of hydrochlorothiazide on the 5th day (mg)	20 ± 40	18 ± 28	0.747	23 ± 40	14 ± 27	0.171
Worsening renal function	52.0%	34.0%	0.069	52.0%	33.3%	0.062
In-hospital inotropes or vasopressors	4.0%	9.8%	0.436	6.0%	8.2%	0.715
Length of stay (days)	9.4 ± 5.8	8.4 ± 4.7	0.319	9.9 ± 6.0	7.8 ± 4.1	0.039

NT-proBNP, N-terminal pro-brain natriuretic peptide; UNa, urinary sodium; VAS, visual analogue scale.

Figure 2 Outcomes in de novo HF and ADHF based on preadmission dose of furosemide. Survival (A) and event-free (death or HF readmission) survival (B) were compared between de novo HF, ADHF with preadmission dose of furosemide ≤ 80 mg, and ADHF with preadmission dose of furosemide > 80 mg.

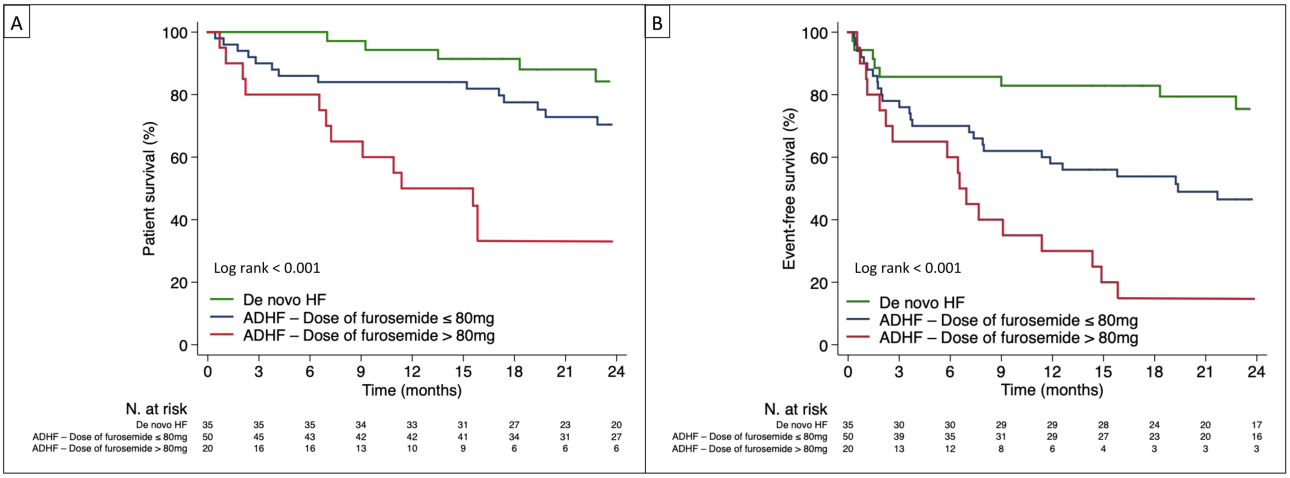
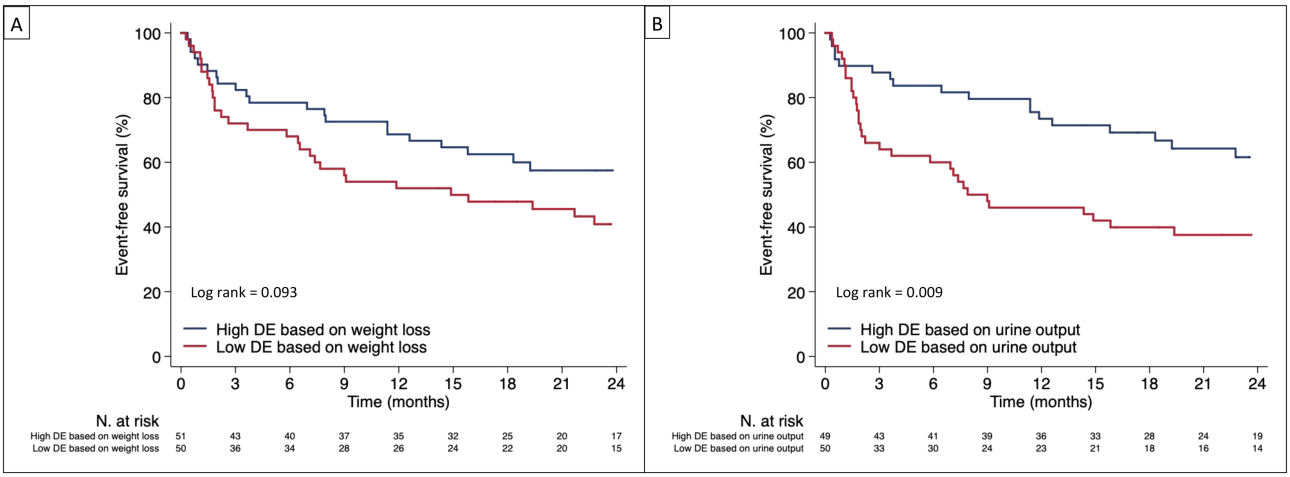


Figure 3 Event-free (death or HF readmission) survival in low vs. high diuretic efficiency based on weight loss (A) and based on urine output (B).



In the univariate Cox regression analysis, dyslipidaemia, previous HF diagnosis, higher dose of furosemide before admission, lower glomerular filtration rate at admission, higher NT-proBNP at admission, decrease in NT-proBNP ≤ 30%, lower increase in haemoglobin, and lower DE based on both weight loss and urine output were associated with mortality or HF readmission. However, in the multivariate analysis, only previous HF diagnosis, NT-proBNP at admission, decrease in NT-proBNP ≤ 30%, and DE based on weight loss were independent predictors of mortality or HF readmission. We also performed a multivariate Cox regression analysis in ADHF patients (excluding de novo HF): the dose of furosemide before admission and NT-proBNP at admission were independently associated with mortality or HF readmission (*Table 4*).

Discussion

The analysis of the REDIHF registry showed that more advanced disease, low blood pressure, renal dysfunction, anaemia, and high preadmission dose of diuretics are predictors of low DE in acute HF. Furthermore, low DE was associated with a lesser decongestion. The dose of furosemide before admis-

Table 4 Univariate and multivariate Cox regression analysis for mortality or HF readmission in the whole cohort and in ADHF cohort

	All patients (n = 105)				Acute decompensated heart failure (n = 70)			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (years)	1.00 (0.98–1.03)	0.814			0.99 (0.96–1.02)	0.504		
Male sex	0.99 (0.57–1,71)	0.982			1.37 (0.75–2.52)	0.305		
Arterial hypertension	1.03 (0.49–2.19)	0.934			0.72 (0.30–1.70)	0.446		
Diabetes mellitus	1.20 (0.71–2.05)	0.483			1.15 (0.64–2.05)	0.639		
Dyslipidaemia	2.02 (1.09–3.77)	0.026	NS		1.55 (0.80–3.01)	0.192		
De novo heart failure	0.33 (0.16–0.65)	0.001	0.38 (0.18–0.79)	0.010				
Atrial fibrillation	1.36 (0.78–2.36)	0.275			1.23 (0.66–2.28)	0.519		
Significant coronary artery disease[a]	1.07 (0.61–1.87)	0.806			1.13 (0.63–2.05)	0.683		
LVEF < 40%	1.42 (0.83–2.41)	0.191			1.34 (0.75–2.39)	0.326		
Beta-blocker before admission	1.06 (0.58–1.96)	0.829			0.47 (0.22–1.02)	0.055	NS	
ACE inhibitor or ARB before admission	0.88 (0.52–1.48)	0.622			1.08 (0.60–1.93)	0.799		
Sacubitril/valsartan before admission	1.59 (0.68–3.73)	0.282			1.12 (0.48–2.65)	0.793		
MRA before admission	1.18 (0.66–2.11)	0.578			1.01 (0.55–1.89)	0.966		
Dose of furosemide before admission (per 40 mg)	1.44 (1.21–1.71)	<0.001	NS		1.33 (1.08–1.65)	0.007	1.34 (1.08–1.67)	0.009
Thiazide before admission	0.98 (0.50–1.95)	0.964			1.15 (0.51–2.57)	0.737		
Systolic blood pressure at admission (mmHg)	0.99 (0.98–1.01)	0.592			0.99 (0.98–1.01)	0.334		
Heart rate at admission (b.p.m.)	0.99 (0.98–1.01)	0.700			1.00 (0.98–1.01)	0.871		
Haemoglobin at admission (g/dL)	0.89 (0.78–1.02)	0.087	NS		0.88 (0.76–1.02)	0.081		
Sodium at admission (mmol/L)	1.01 (0.94–1.08)	0.737			1.02 (0.95–1.10)	0.559		
Glomerular filtration rate at admission (mL/min/1.73 m^2)	0.98 (0.97–1.00)	0.018	NS		0.99 (0.98–1.01)	0.192		
Creatinine at admission (mg/dL)	1.64 (1.11–2.42)	0.013	NS		1.61 (1.01–2.56)	0.047	NS	
Albumin at admission (g/dL)	0.88 (0.50–1.56)	0.662			0.75 (0.42–1.37)	0.350		
GGT at admission (U/L)	1.00 (0.99–1.01)	0.128			1.00 (1.00–1.01)	0.804		
Bilirubin at admission (mg/dL)	1.28 (0.89–1.85)	0.181			0.87 (0.57–1.34)	0.534		
NT-proBNP at admission (per 1000 pg/mL)	1.04 (1.02–1.07)	<0.001	1.08 (1.04–1.12)	<0.001	1.03 (1.01–1.06)	0.004	1.03 (1.01–1.06)	0.004
Urine output per unit of furosemide (per 100 mL/40 mg)	0.93 (0.88–0.98)	0.007	NS		0.96 (0.91–1.02)	0.153		
Weight loss per unit of furosemide (per 100 g/40 mg)	0.94 (0.89–1.00)	0.038	0.91 (0.85–0.98)	0.009	0.93 (0.86–1.00)	0.054	NS	
UNa on the 5th day (mEq/L)	1.00 (0.99–1.01)	0.795			1.00 (0.99–1.01)	0.774		
Decrease in NT-proBNP > 30%	0.52 (0.30–0.89)	0.016	0.45 (0.25–0.83)	0.010	0.69 (0.38–1.27)	0.232		
Change in haemoglobin on the 5th day (g/dL)	0.78 (0.63–0.97)	0.026	NS		0.82 (0.65–1.04)	0.102		
Lack of B-lines in lung ultrasound on the 5th day	0.67 (0.37–1.22)	0.193			0.72 (0.38–1.39)	0.333		

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NS, not significant; NT-proBNP, N-terminal pro-brain natriuretic peptide; UNa, urinary sodium.

[a]Significant coronary artery disease was defined by invasive coronary angiography as >50% stenosis of the left main coronary artery or >70% stenosis in a major coronary vessel.

sion seems better to predict DE based on urine output than weight loss. Both previous outpatient dose of furosemide, NT-proBNP levels, and DE based on weight loss were independent predictors of HF readmission or mortality.

Determinants of low diuretic efficiency

More advanced disease, low blood pressure, renal dysfunction, anaemia, and high preadmission dose of diuretics were predictors of low DE. Similar results have been seen in other studies.[6–8,10,11] First, renal dysfunction is common among patients hospitalized with acute HF and is an important determinant of diuretic response.[6,18] Diuretic exerts their effects via the kidney, relying on secretion to achieve the tubule. Renal dysfunction is associated with reduced diuretic secretion and consequently worse urinary diuretic delivery. However, defects at the level of the renal tubule are more important than reduced diuretic delivery in determining DR.[19] Second, it would appear reasonable that more advanced disease and low blood pressure predict low DE, as they are linked to chronic kidney disease and higher doses of diuretics. Third, anaemia in HF has been associated with increased severity of HF, progressive worsening of renal function, and the need for higher doses of diuretics.[20] Therefore, it is not surprising that anaemia was associated with low DE in our study. Finally, as will be explained below, a high outpatient dose of furosemide before admission predicts low DE. However, the treatment with mineralocorticoid receptor antagonists did not affect DE in our study. This is not surprising, given that in the ATHENA-HF trial, high-dose spironolactone use was not associated with greater congestion improvement, urine output, weight loss, or clinical outcomes.[21]

Decongestion and low diuretic efficiency

Congestion evaluation is key in the therapeutic management of acute HF. Given that physical examination has some limitations in the assessment of decongestion, several biomarkers and lung ultrasound parameters have been proposed as essential tools to guide diuretic treatment. We assessed change in NT-proBNP, hemoconcentration, and lung ultrasound, as they had shown to predict outcomes in acute HF.[22–24] Patients with low DE, as could be expected, had lesser decongestion measured by all these methods. Surprisingly, residual congestion measured by physical examination was similar in high vs. low DE patients. This may be because it was collected as a dichotomized variable, and there is considerable subjectivity in its measurement.

Dose of furosemide before admission and diuretic efficiency

Loop diuretic agents inhibit NaCl reabsorption in the thick ascending limb, thereby increasing the luminal NaCl concentration in fluid entering the distal convoluted tubule. However, chronic diuretic treatment increases the capacity of the distal nephron to reabsorb delivered NaCl, leading to a decline in natriuresis ('braking phenomenon').[25] In our study, the previous outpatient dose of furosemide helped predict low DE in acute HF, especially with regard to DE based on urine output. In fact, the latter had a weak to moderate correlation with the previous dose of furosemide. This supports the current recommendation of treating patients on an ambulatory diuretic regimen with at least the pre-existing oral dose administered intravenously.[3] Furthermore, the DOSE-AHF trial demonstrated that high loop diuretic dose (2.5 usual home dose) compared with low dose (equal to home dose) resulted in higher dyspnoea relief, weight loss, and net fluid loss.[26] Worsening renal function occurred more in the high-dose arm. However, subsequent analyses showed that an initial rise in plasma creatinine was associated with better, rather than worse, long-term clinical outcomes.[27] Therefore, the outpatient dose of furosemide before admission and renal function should be critical when deciding on the initial diuretic dose in acute HF.

Diuretic resistance and long-term outcomes

Several post hoc analyses from different clinical trials in acute HF have shown that poor DE is associated with HF readmission and mortality.[7,8,11] Our results also showed this association in a real-world population with acute HF, that is, older patients, those with preserved LVEF, or those with several comorbidities. However, an even more important finding was the usefulness of the outpatient dose of furosemide before admission to predict long-term outcomes. In this sense, it should be noted that its ability to predict HF readmission or mortality in ADHF was independent of DE during hospitalization. Moreover, it is easily obtained and available in all patients at admission, so its usefulness in clinical practice is assured. A daily dose of furosemide $>$ 80 mg was associated with poor outcomes in chronic HF in previous studies.[13,14,28,29] It was a good cut-off point at admission to predict mortality or HF rehospitalization in our study. Moreover, it should be noted that for each extra 40 mg of furosemide, we observed a 34% increased risk of events. This was also observed in a post hoc analysis from the DOSE trial that showed that previous furosemide dose $\geq$ 120 mg in ADHF was associated with increased risk of HF readmission or death at 60 days.[30]

Limitations

Several limitations of this study are worth noting. First, the small sample size was the main limitation. In spite of this, however, patients were rigorously evaluated during hospitalization, and different methods to assess diuretic response and congestion were used. Thus, we consider that the present study provides important information about DR in acute HF. Second, contrary to other studies, lower urinary sodium was not associated with worse outcomes. This was probably because it was measured before loop-diuretic administration. Recent studies have shown the prognostic value of spot urinary sodium after diuretic administration.[31,32] In fact, we recently described that low natriuresis after a furosemide stress test identifies patients at a higher risk of inadequate diuretic response and worse outcomes.[33] Third, congestion measured by physical examination was collected as a dichotomized variable. Therefore, we did not assess the degree of congestion at admission or after diuretic treatment by this method. Fourth, fluid intake and net fluid loss were not measured. We took this decision because a previous study showed that the correlation between weight and net fluid loss is modest and that the latter systematically overestimates weight loss.[12] This is probably explained by inaccuracies in fluid intake determination and errors in the estimation of insensible water loss. Fifth, even though the dose of loop and thiazide diuretics was collected, the pathophysiology of diuretic response is complex and multifactorial; this makes difficult to exclude confounding factors such as diuretic effect from other drugs, medical interactions, and, given its dynamic nature, variations in DR during hospitalization. Sixth, follow-up after the 2 month visit was telematic. However, we had access to medical reports in all patients and no patient was lost to follow-up. Finally, even though the COVID-19 pandemic has collapsed the health care system and caused the deaths of thousands of people in our country, no patient died from COVID-19 during the study period.

Conclusions

More advanced disease, low blood pressure, renal dysfunction, anaemia, and higher preadmission dose of diuretics predict low DE during hospitalization. Outpatient dose of furosemide and renal function must be taken into account when deciding on the initial diuretic dose in acute HF. Furthermore, low DE is associated with a lesser decongestion measured by NT-proBNP, hemoconcentration, and lung ultrasound. Concerning prognosis, de novo HF patients have fewer events during follow-up. In ADHF, the outpatient dose of furosemide before admission can predict long-term prognosis better than DE during hospitalization.

Conflict of interest

None of the authors have any conflicts of interest to disclose.

Funding

None.

Supporting information

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

Figure S1: Correlation between previous dose of furosemide and DE based on weight loss (A) or DE based on urine output (B). Correlation between DE based on weight loss and based on urine output (C).

Figure S2: ROC curve of dose of furosemide before admission to predict low diuretic efficiency based on weight loss (A) and urine output (B).

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