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Original Paper

Lack of Diuretic Efficiency (but Not Low Diuresis) Early in An Acutely Decompensated Heart Failure Episode Is Associated with Increased 180-Day Mortality

João Pedro Ferreira[a, b] Nicolas Girerd[a] Pedro Bettencourt Medeiros[c] Miguel Bento Ricardo[c] Tiago Almeida[c] Alexandre Rola[c] Faiez Zannad[a] Patrick Rossignol[a] Irene Aragão[d]

[a]INSERM, Centre d'Investigations Cliniques Plurithématique 1433, INSERMU1116, Université de Lorraine, CHRU de Nancy, F-CRIN INI-CRCT, Vandoeuvre-lès-Nancy, France; [b]Cardiovascular Research and Development Unit, Department of Physiology and Cardiothoracic Surgery, Faculty of Medicine, University of Porto, and [c]Internal Medicine Department and [d]Intensive Care Unit, Centro Hospitalar do Porto, Porto, Portugal

Keywords
Diuretic efficiency · Diuresis · Survival · Acutely decompensated heart failure

Abstract
Introduction: The assessment of the amount of urine produced by the dose of administered diuretic has been proposed as the main signal of interest in diuretic responsiveness – diuretic efficiency (DE). The main aim of our study is to determine if a low DE is associated with 180-day all-cause mortality (ACM). ***Methods:*** During a 3-year period, we retrospectively studied patients with acutely decompensated heart failure (ADHF) and respiratory insufficiency admitted to the emergency room of a tertiary university hospital in Porto, Portugal. A total of 170 patients (age 76.2 ± 10.3 years) were included. The outcome of ACM occurred in 43 (25.3%) patients during the 180-day follow-up period. DE was evaluated for a maximum of 3 h after emergency room admission. The lowest DE was defined as ≤140 mL of diuresis per 40 mg of furosemide equivalents. ***Results:*** No significant differences in age, comorbidities, baseline HF symptoms, or disease-modifying medication were found between the lowest and highest DE groups. The lowest DE group had higher blood urea and lower estimated glomerular filtration rate (eGFR) levels (41.3 ± 24.5 vs. 56.7 ± 23.2 mL/min/1.73 m^2, $p < 0.001$). The patients with the lowest DE had significantly higher rates of ACM during the 180-day follow-up, even after adjustment for other clinically relevant variables: hazard ratio (HR) [95% CI] = 2.31 [1.16–4.58], $p = 0.016$. The lowest diuresis (≤300 mL) and the highest intravenous furosemide dose (>80 mg) alone were not significantly associated with the outcome. After adjustment for N-termi-

Dr. João Pedro Ferreira
Centre d'Investigations Cliniques-INSERM CHU de Nancy
Institut Lorrain du Cœur et des Vaisseaux Louis Mathieu
4 Rue du Morvan, FR–54500 Vandoeuvre-lès-Nancy (France)
E-Mail j.ferreira@chru-nancy.fr

nal prohormone of brain natriuretic peptide, the association between the lowest DE and the outcome lost strength (HR [95% CI] = 1.53 [0.75–3.13], p = 0.240). ***Conclusion:*** A low DE (≤140 mL/40 mg of furosemide) in the first 3 h after an ADHF episode was associated with increased mid-term mortality rates.

Introduction

Urgent fluid removal is the main goal doctors pursue from the very first contact with an acute pulmonary edema/acutely decompensated heart failure (ADHF) episode [1, 2]. The mainstay of therapy to obtain fluid removal is intravenous (IV) loop diuretics, mainly furosemide [3–5]. Unfortunately, an efficient diuretic response is not observed in many patients who present with ADHF, and the lack of diuretic response is associated with adverse events during and after hospitalization [6, 7]. However, diuretic response is itself hard to evaluate, and neither diuretic dose nor diuresis are good surrogate markers to evaluate the response to diuretics [8–10].

Assessment of the amount of urine produced by the dose of administered diuretic has been proposed as the main signal of interest in diuretic responsiveness, i.e., the efficiency with which the diuretic can facilitate urine production (and not the absolute dose of diuretic or the absolute production of urine) is the primary signal to determine diuretic efficiency (DE) [11]. The simple measure of DE allows the adjusted metric measurement of the urine produced to a given diuretic dose. Importantly, a low DE during ADHF hospitalization was associated with poorer long-term outcomes in 2 selected cohorts [11]. However, if DE determined in the first few hours of an ADHF episode is associated with worse outcomes is yet to be seen. This easy and inexpensive measurement could be very informative to clinicians, since important decisions must be performed early in an ADHF event (e.g., therapy escalation, department allocation, resources management, and patient/family expectations).

The aims of our study are (1) to characterize the patients with a low DE within the first 3 h of a severe ADHF episode; (2) to determine if a low DE is associated with 180-day all-cause mortality (ACM), and (3) to compare (head-to-head) DE with diuresis and diuretic dose in prognostic association.

Methods

Studied Population, Emergency Room Description, and Oversight

During a 3-year period (from January 2012 to December 2014), we retrospectively studied all patients with ADHF admitted to the Emergency Room (ER) of Centro Hospitalar do Porto (CHP), Porto, Portugal, which is a tertiary university hospital. This ER of CHP has some particularities that should be noticed. The ER is situated inside the Urgency Department under the supervision of the Intensive Care Unit. The ER is equipped with ventilators and invasive monitorization devices in order to receive unstable/severe patients. Patients can be closely monitored, and noninvasive ventilation can be performed safely with the possibility to perform invasive ventilation, if required. All patients admitted to this subunit have urinary catheters inserted. Diuresis, vital signs, physical examination, and treatments are recorded in a specific board. The patients described in this cohort have all been admitted for ADHF/pulmonary edema with associated respiratory insufficiency (PaO_2/FIO_2 <300). Upon ER admission, all patients had high-concentration non-rebreathing masks with FIO_2 ≈80%.

All authors designed the study. The first, third, fourth, fifth, and sixth authors collected and registered the data. The first 2 authors performed the statistical analysis and wrote the first draft of the manuscript. All authors edited and approved the manuscript and assume full responsibility for the accuracy and completeness of the data and for the fidelity of this report to the study protocol.

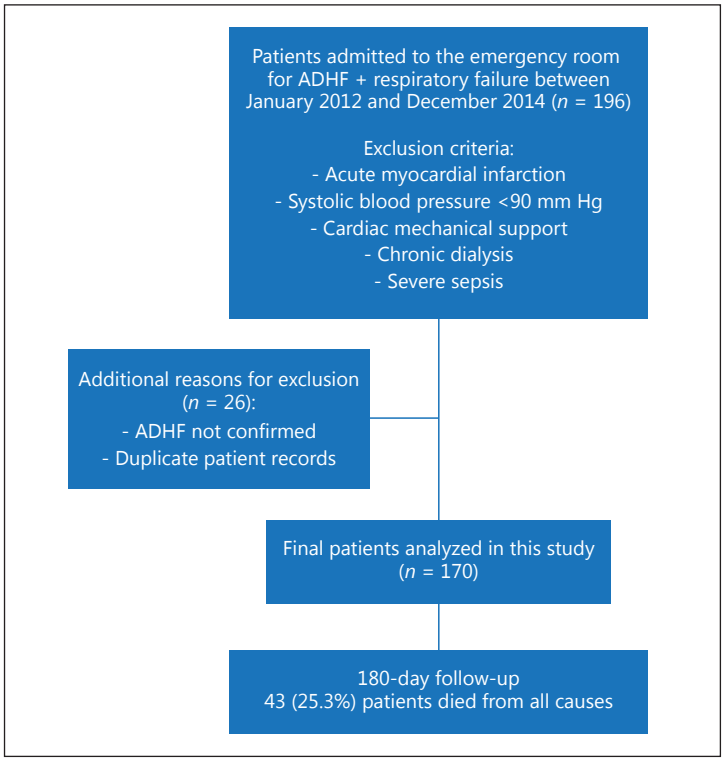

Fig. 1. Study flowchart. ADHF, acutely decompensated heart failure.

Criteria and Definitions

Patients with ADHF criteria were included. The diagnosis of ADHF was performed according to the European Society of Cardiology (ESC) criteria, defined as a rapid or gradual onset of signs and symptoms of worsening HF resulting in unplanned hospitalization (including new onset acute HF) [9, 12]. We used associated elevated natriuretic peptides (NPs) to adjudicate hospitalization whenever possible (83.5% of the cases). An echocardiographic study was performed on all patients during the index hospitalization. Left ventricular ejection fraction (LVEF) was measured by Simpson's biplane method. We excluded patients with acute myocardial infarction, refractory hypotension, cardiac mechanical support, chronic dialysis, and severe sepsis in order to mitigate inclusion bias and to have a uniform dataset of severe ADHF patients.

Patient cases were registered in a uniform database based on the information collected from the clinical records/reports. The study included cases from both community and referral hospitals. Underlying diseases, precipitating factors, clinical presentation, most recent echocardiography findings, and analytical results (including hemoglobin, electrolytes, plasma creatinine and urea, and N-terminal prohormone of brain natriuretic peptide [NT-pro BNP]) were registered at admission (i.e., first available data).

Diuresis was retrospectively assessed by the ER registries, which provide information regarding diuresis and medications. Diuresis and diuretics performed outside the hospital (i.e., in the ambulance and/or at home) were inconsistently recorded (of notice, ambulance transportation in Porto usually takes less than 15 min until hospital arrival). All patients had urinary catheters inserted upon ER admission. Some of these patients possibly had (not registered) urinary catheters inserted before ER admission (i.e., in the ambulance during transportation), but, as stated above, this represents a gap of <15 min.

Diuresis and diuretic doses were registered in the ER from arrival to a maximum of 3 h after ER admission. We capped registries at 3 h to assess the prognostic value very early upon admission. This information inconsistency reflects daily clinical practice in an emergency context.

We contacted the patients and/or their families who had been lost from electronic registries in order to incorporate real, unbiased prognostic information. The studied endpoint was ACM. Hospital admission for ADHF was defined according to the most recent guidelines [13]. The follow-up period was 180-days counting from hospital admission.

The study was carried out in accordance with the Declaration of Helsinki and approved by the institutional ethics committee. The study flowchart is provided in Figure 1.

Statistical Analysis

The results are provided as mean ± standard deviation for continuous variables with a normal distribution or as median (25th–75th percentile) if the distribution was skewed. Normality assumption was checked by visual discretion. Categorical variables were expressed in absolute numbers (*n*) and proportions (%).

Due to the lack of standardized cutoffs in the literature and the great dispersion of the variables in the upper values, DE and diuresis were divided in tertiles. The upper 2 tertiles were merged because they showed the same information regarding prognosis, hence, DE was divided in ≤140 mL per 40 mg of furosemide equivalents (i.e., 40 mg = 1, 80 mg = 2, 120 mg = 3, and so on) versus >140 mL per 40 mg of furosemide equivalents, and diuresis was divided in ≤300 versus >300 mL. IV furosemide was dichotomized in high versus low dose (>80 vs. ≤80 mg).

Population characteristics were compared using the independent sample t test for normally distributed continuous variables, the Mann-Whitney test for skewed variables, and the χ^2 test for categorical variables.

The primary outcome was ACM. Univariable time-to-event comparisons were made using the log-rank test and univariable Cox proportional hazards models. Survival was estimated with the Kaplan-Meier method. Cox proportional-hazards models were used to obtain unadjusted and covariate adjusted hazard ratios. Proportional hazards assumptions were checked. Covariates used for adjusted hazards ratios were chosen from demographic, clinical, and laboratorial variables that have been previously found to be clinically relevant. All continuous variables included in the model were checked for linearity.

Statistical analyses were performed using SPSS 23 software (IBM SPSS Statistics for Windows, Version 23.0., released in 2013; IBM Corp., Armonk, NY, USA).

A p value <0.05 was considered statistically significant (including for interaction).

Results

Outpatient Characteristics of the Study Population

No significant differences in age, comorbidities, baseline HF symptoms, or disease-modifying medication were found between the lowest and highest DE groups; however, the lowest DE group had a higher mean oral furosemide dose (68.2 ± 53.1 vs. 52.4 ± 41.3 mg, p = 0.044), but without differences in the proportion of patients who received >40 mg of furosemide per day (Table 1).

Early-Admission Clinical Assessment

No significant differences in congestion signs or vital parameters were found between the lowest and highest DE groups. As expected, the lowest DE group had a lower diuresis and a higher IV furosemide dose ($p < 0.01$ for both) (Table 1). The lowest DE group also had higher blood urea and creatinine levels and a lower estimated glomerular filtration rate (eGFR; 41.3 ± 24.5 vs. 56.7 ± 23.2 mL/min/1.73 m^2, $p < 0.001$). The mean serum potassium levels and the proportion of patients in whom morphine was administered were also higher in the lowest DE group (4.59 ± 0.80 vs. 4.17 ± 0.71 mmol/L, $p = 0.001$ and 74.5 vs. 57.3%, $p = 0.037$, respectively) (Table 1).

Discharge Clinical Assessment

At discharge, patients with the lowest DE had a trend to present peripheral edema more frequently (33.3 vs. 19.8%, $p = 0.077$). No significant differences were observed regarding discharge medications (Table 1).

In-Hospital Evolution

The proportion of patients with worsening renal function and NT-pro BNP drop >30% during hospitalization was not different between the lowest and highest DE groups; however, the proportion of missing NT-pro BNP values (35.9%) was important (Table 1).

Table 1. Characteristics of the study population globally and according to diuretic efficiency

Variables	Total (N = 170)	Lowest DE (≤140 mL/40 mg) (n = 51)	Highest DE (>140 mL/40 mg) (n = 103)	p value	% mv
Demographics and medical history					
Age, years	76.2±10.3	76.0±10.2	76.4±10.2	0.820	0
Male sex	85 (50)	24 (47.1)	52 (50.5)	0.689	0
Hypertension	148 (87.1)	44 (86.3)	90 (87.4)	0.848	0
Diabetes mellitus	90 (52.9)	29 (56.9)	52 (50.5)	0.456	0
COPD	34 (20)	10 (24.4)	19 (20.7)	0.630	12.4
AFib	80 (47.1)	26 (51.0)	48 (46.6)	0.609	0
Heart failure characterization					
Ischemic etiology	96 (56.5)	33 (64.7)	56 (54.4)	0.222	0
LVEF, %	43.8±11.1	42.3±10.3	44.5±11.5	0.235	0
LVEF <40%	65 (38.2)	22 (43.1)	34 (33.0)	0.219	
Beta-blockers	100 (58.8)	33 (64.7)	60 (58.3)	0.441	5.3
ACEi/ARBs	119 (70)	37 (72.5)	72 (69.9)	0.734	0
MRAs	23 (13.5)	7 (13.7)	15 (14.6)	0.889	0
Furosemide dose, mg	55.4±45.4	68.2±53.1	52.4±41.3	**0.044**	0
Furosemide >40 mg/day	75 (44.1)	26 (51.0)	44 (42.7)	0.333	
First vital signs, diuresis, and clinical assessment of congestion upon emergency room admission					
Peripheral edema	99 (58.2)	29 (58.0)	62 (60.2)	0.795	0.6
Interstitial edema X-ray	168 (98.8)	50 (98.0)	103 (100)	0.154	0
Pleural effusion X-ray	93 (54.7)	28 (56.0)	54 (52.4)	0.678	0.6
Noninvasive ventilation	145 (85.3)	45 (88.2)	89 (86.4)	0.751	0
PaO_2/FIO_2 ratio	165±86	175±97	165±83	0.448	0.6
Heart rate, bpm	108±28	108±27	108±30	0.987	0
SBP, mm Hg	162±33	161±32	164±35	0.669	0
Diuresis first 3 h, mL	420 (240–705)	200 (100–280)	530 (400–960)	**<0.001***	9.4
Lowest diuresis (≤300), mL	56 (32.9)	42 (82.4)	12 (11.7)	**<0.001**	
IV furosemide dose first 3 h, mg	91±48	119±59	81±34	**<0.001**	1.2
IV furosemide >80 mg	68 (40)	32 (62.7)	34 (33)	**<0.001**	
DE first 3 h, mL/40mg	211 (119–378)	73 (37–120)	300 (210–480)	**<0.001***	9.4
Day 1 biochemical data					
Urea, mg/dL	71.5±48.4	87.0±58.3	61.0±32.6	**<0.001**	0
Creatinine, mg/dL	1.56±1.17	2.00±1.40	1.28±0.62	**<0.001**	0
eGFR, mL/min/1.73 m^2	51.1±24.8	41.3±24.5	56.7±23.2	**<0.001**	1.7
Sodium, mmol/L	137.5±5.1	137.3±4.9	137.9±5.0	0.500	0
Potassium, mmol/L	4.34±0.82	4.59±0.80	4.17±0.71	**0.001**	0
Albumin, mg/dL**	3.6±0.6	3.5±0.6	3.6±0.5	0.223	25.9
NT-pro BNP/100, pg/mL	39 (16–79)	51 (16–114)	36 (14–71)	0.235*	16.5
Hemoglobin, g/dL	12.5±2.2	12.2±2.2	12.5±2.1	0.453	0.6
Day 1 medications (except furosemide) and procedures					
Morphine	103 (60.6)	38 (74.5)	59 (57.3)	**0.037**	0
Nitrates	139 (81.8)	44 (86.3)	82 (79.6)	0.313	0
Beta-blockers	111 (65.3)	35 (68.6)	66 (64.1)	0.576	0
ACEi/ARBs	100 (58.8)	31 (60.8)	60 (58.3)	0.764	0
MRAs	49 (28.8)	17 (33.3)	29 (28.2)	0.509	0
Discharge clinical assessment of congestion					
Peripheral edema	35 (20.5)	16 (33.3)	18 (19.8)	0.077	18.2
Interstitial edema X-ray	42 (24.7)	13 (43.3)	26 (35.6)	0.483	39.4
Pleural effusion X-ray	22 (12.9)	7 (15.9)	10 (10.5)	0.368	39.4

Table 1 (continued)

Variables	Total (*N* = 170)	Lowest DE (≤140 mL/40 mg) (*n* = 51)	Highest DE (>140 mL/40 mg) (*n* = 103)	*p* value	% mv
Discharge medications					
Oral furosemide dose, mg	70±43	77±50	68±41	0.303	8.2
Furosemide >40 mg/day	140 (82.4)	37 (86)	88 (90.7)	0.409	
Beta-blockers	101 (59.4)	30 (71.4)	61 (62.9)	0.331	8.8
ACEi/ARBs	92 (54.1)	27 (62.8)	55 (56.7)	0.500	8.2
MRAs	37 (21.8)	12 (27.9)	21 (21.6)	0.421	8.2
In-hospital evolution					
WRF	20 (13.0)	8 (15.7)	12 (11.7)	0.483	9.4
NT-pro BNP >30% drop	40 (36.7)	14 (42.2)	26 (34.2)	0.414	35.9
Events					
180-day ACM	43 (25.3)	19 (37.3)	22 (21.4)	**0.036**	0

Values are presented as n (%), mean ± standard deviation, or median (range). DE, diuretic efficiency. Lowest DE: ratio diuresis (mL) to furosemide (by 40 mg) ≤140 mL/40 mg, i.e., lowest tertile; highest DE, ratio diuresis (mL) to furosemide (by 40 mg) >140 mL/40 mg, i.e., highest 2 tertiles. COPD, chronic obstructive pulmonary disease; AFib, atrial fibrillation; SBP, systolic blood pressure; IV, intravenous; LVEF, left ventricular ejection fraction; ACEi/ARBs, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; MRAs, mineralocorticoid receptor antagonists; NT-pro BNP, N-terminal prohormone of brain natriuretic peptide; WRF, worsening renal function (defined as >20% drop in the estimated glomerular filtration rate [eGFR] during hospitalization); ACM, all-cause mortality. eGFR was calculated by the CKD-EPI creatinine equation [31]. Bold values indicate significance (p ≤ 0.05). * Nonparametric Mann-Whitney test. ** First measure during hospitalization.

Association of DE with ACM

Patients with the lowest DE (≤140 mL/40 mg furosemide) had significantly higher rates of ACM during the 180-day follow-up, even after adjustment for other clinically relevant variables (age, sex, eGFR, LVEF, and basal furosemide; hazard ratio [HR] (95% CI), 2.31 (1.16–4.58), p = 0.016. The Lowest diuresis (≤300 mL) and highest IV furosemide dose (>80 mg) alone were not significantly associated with the outcome (HR [95% CI], 1.56 [0.84–2.89], *p* = 0.159 and 1.05 [0.57–1.92], *p* = 0.884, respectively) (Table 2, Fig. 2).

After adjustment for NT-pro BNP, the association between the lowest DE and the outcome lost strength (HR [95% CI], 1.53 [0.75–3.13], p = 0.240) (Table 2).

Subgroup Analysis

Subgroup analysis (by median values of: eGFR <50 vs. >50 mL/min/1.73 m^2; basal furosemide <40 vs. >40 mg/day; NT-pro BNP/100 <39 vs. >39 pg/mL) did not show significant "interactions" between the subgroups, and the direction of the association was retained in all subgroups; however, with lower precision than in the overall population (Table 3).

Discussion

Our study demonstrated that patients with a lower DE (≤140 mL/40 mg furosemide) in the first 3 h after a severe ADHF episode had an increased risk of mid-term mortality that was independent of age, sex, renal function, LVEF, or the basal furosemide dose. However, NT-pro BNP was an important confounder reflecting the critical role played by increased neurohor-

Table 2. Cox regression models for the association of diuretic efficiency with all-cause mortality

	Hazard ratio (95% CI)	*p* value
Univariable		
Lowest DE, ≤140 mL/40 mg	1.96 (1.06–3.61)	**0.032**
Lowest diuresis (≤300), mL	1.56 (0.84–2.89)	0.159
Highest IV furosemide (>80), mg	1.05 (0.57–1.92)	0.884
Model 1		
Lowest DE, ≤140 mL/40 mg	2.08 (1.12–3.85)	**0.020**
Lowest diuresis (≤300), mL	1.53 (0.82–2.83)	0.180
Highest IV furosemide (>80), mg	1.12 (0.61–2.06)	0.713
Model 2		
Lowest DE, ≤140 mL/40 mg	2.31 (1.16–4.58)	**0.016**
Lowest diuresis (≤300), mL	1.60 (0.81–3.15)	0.173
Highest IV furosemide (>80), mg	1.04 (0.56–1.93)	0.903
Model 3		
Lowest DE, ≤140 mL/40 mg	1.53 (0.75–3.13)	0.240
Lowest diuresis (≤300), mL	1.35 (0.66–2.74)	0.411
Highest IV furosemide (>80), mg	0.82 (0.40–1.67)	0.598

DE, diuretic efficiency. Highest DE and diuresis tertiles were used as the reference category. The lowest intravenous (IV) furosemide binary category was used as the reference. The dependent variables represent the cumulative values of the first 3 h of medical contact (in or outside the hospital). Lowest DE, ratio diuresis (mL) to furosemide (by 40 mg) ≤140 mL/40 mg, i.e., lowest tertile; highest DE, ratio diuresis (mL) to furosemide (by 40 mg) >140 mL/40 mg, i.e., highest two tertiles); CI, confidence interval. Model 1, adjusted to sex and age; Model 2, adjusted to Model 1 + estimated glomerular filtration rate, left ventricular ejection fraction and basal furosemide dose; Model 3, adjusted to Model 1 + N-terminal prohormone of brain natriuretic peptide/100 above the median of 39 pg/mL. Bold values indicate significance ($p \leq 0.05$).

monal activation in these hyperacute patients. Diuresis and IV furosemide dose per se were not significantly associated with the outcome. These findings provide an easily calculated metric that strongly associates with mortality and may have advantage over the diuretic dose or diuresis in describing diuretic resistance.

Loop Diuretics, Urine Production, and Outcomes

A single administration of 40 mg of furosemide produces maximal instantaneous natriuresis in healthy volunteers [14]. However, patients with advanced age, symptomatic HF, renal dysfunction, higher levels of natriuretic peptides, a lower LVEF, and higher doses of diuretics in the ambulatory setting are likely to require higher doses of IV diuretics to obtain a satisfactory diuretic response [15–17]. It is well documented that these high-risk patients have higher mortality rates than the lower-risk ones. However, the diuretic doses are not likely to be directly associated with mortality; in fact uptitrated diuretic doses in these high-risk subgroups may be associated with an improved symptom relief, a higher urine output, a greater weight loss, and possibly a survival advantage [8, 18–20]. The absence of causality between the IV diuretic dose and mortality is also supported with evidence derived from prospective trials comparing various modalities of diuretic strategies [3–5, 20, 21]. In accordance to these findings, our study demonstrates that IV furo-

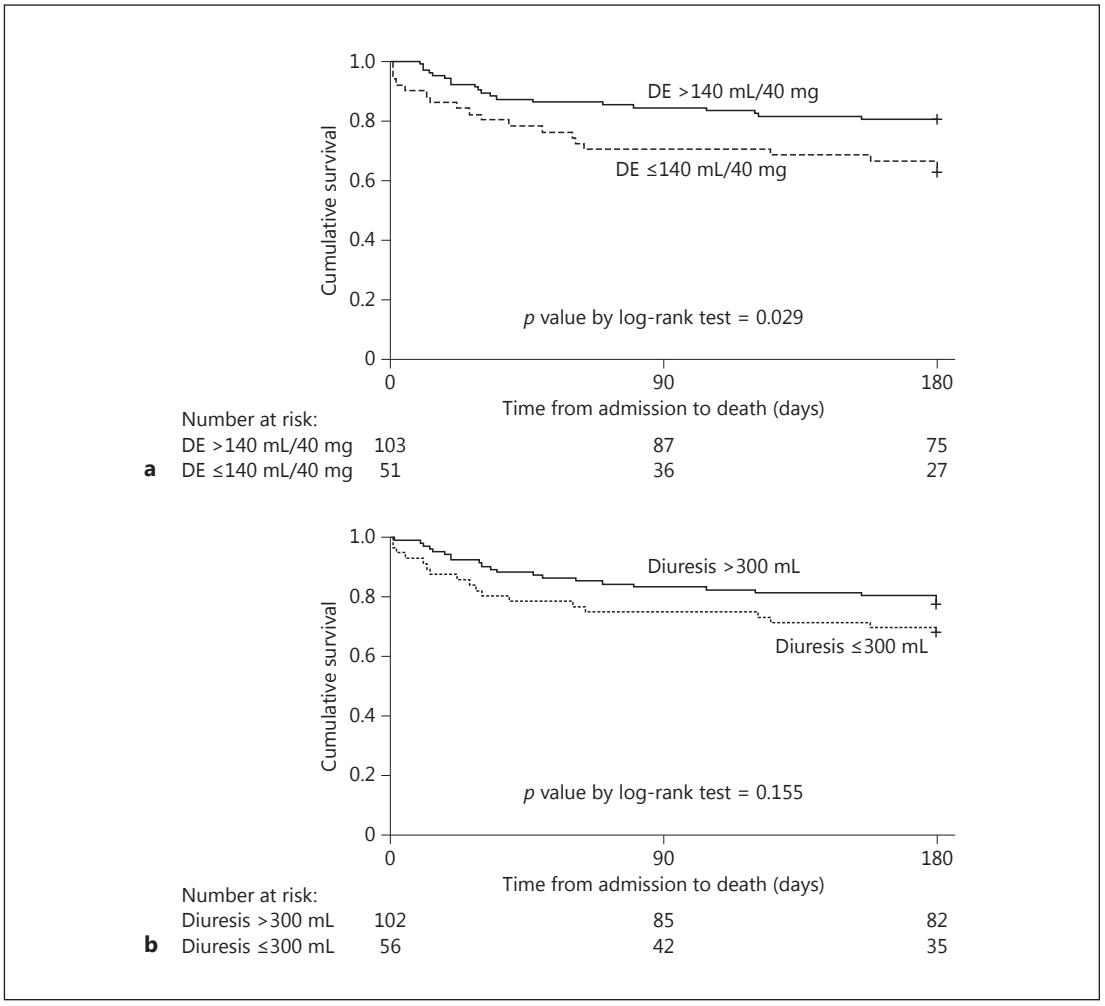

Fig. 2. Kaplan-Meier curves for 180-day mortality according to diuretic efficiency and diuresis. DE, diuretic efficiency.

semide doses were negatively correlated with diuresis, traducing the doctors' perception of severity; i.e., patients with a low urinary output early during an ADHF episode were submitted to higher furosemide doses. However, these high diuretic doses were not associated with mortality.

DE as A Simple and Integrative Diuretic Response Measure

Diuresis itself is also not a good marker of effective decongestion, since it depends on the objectives of fluid loss (e.g., some patients will be effectively decongested with 500 mL of net fluid loss, while others will require 5 L). However, the required diuretic doses to obtain an effective diuresis may greatly vary between ADHF patients, and escalating diuretic doses with persistent worsening HF are worrisome and portend a worse prognosis [3, 22–24]. Hence, DE offers a simple and integrative metric measurement of both sides of the coin: diuresis and diuretic dose. Additionally, a strong and independent association between a low DE during hospitalization and a worsened long-term survival has been demonstrated [11]. On top of this information, our study is the first to demonstrate an association between early diuretic

Table 3. Subgroup analysis for the association of diuretic efficiency with all-cause mortality

Cox regression (events, *n*)		*p* value	*p* for interaction
eGFR ≤50 mL/min/1.73 m^2 (*n* = 21)			0.683
Highest DE	Reference		
Lowest DE	1.76 (0.73–4.24)	0.209	
eGFR >50 mL/min/1.73 m^2 (*n* = 22)			
Highest DE	Reference		
Lowest DE	2.32 (0.96–5.61)	0.061	
Basal furosemide >40 mg/day (*n* = 28)			0.880
Highest DE	Reference		
Lowest DE	1.77 (0.83–3.76)	0.140	
Basal furosemide ≤40 mg/day (*n* = 15)			
Highest DE	Reference		
Lowest DE	1.94 (0.67–5.60)	0.219	
NT-pro BNP/100 >39 pg/mL (*n* = 20)			0.952
Highest DE	Reference		
Lowest DE	1.41 (0.56–3.58)	0.467	
NT-pro BNP/100 ≤39 pg/mL (*n* = 14)			
Highest DE	Reference		
Lowest DE	1.36 (0.46–4.03)	0.584	

DE, diuretic efficiency. Highest DE tertiles were used as the reference category. DE represents the cumulative value of the first 3 h of medical contact (in and outside the hospital). Lowest DE, ratio diuresis (mL) to furosemide (by 40 mg) ≤140 mL/40 mg, i.e., lowest tertile; highest DE, ratio diuresis (mL) to furosemide (by 40 mg) >140 mL/40 mg, i.e., highest 2 tertiles; CI, confidence interval; eGFR, estimated glomerular filtration rate; NT-pro BNP, N-terminal prohormone of brain natriuretic peptide. eGFR was calculated by the CKD-EPI creatinine equation [31].

response (first 3 h after an ADHF episode) and higher mid-term mortality rates. In the present study, no significant differences ("interactions") between "high-risk" subgroups (renal dysfunction, higher basal diuretic doses, and elevated natriuretic peptide levels) were found, and the direction of the hazard ratios towards worse outcomes was maintained, suggesting that early DE is likely to offer similar prognostic information in these "high-risk" subgroups. Nonetheless, we should highlight that NT-pro BNP was an important confounder (without interaction or collinearity within the model). When NT-pro BNP was added to the prognostic model, the associations between a low DE and adverse events lost statistical significance. In concordance to previous findings, these data suggest that increased neurohormonal activation (here represented by NT-pro BNP) plays an important and deleterious role both in DE and the outcome [6, 25, 26].

Clinical Implications

The findings described in this study are derived from a "real-world" cohort of ADHF patients who were admitted to an ER of a tertiary hospital with respiratory insufficiency (without hypotension or acute myocardial infarction). Hence, the management of these patients reflects daily clinical practice. These results can only be generalizable to patients with similar characteristics to those presented in this cohort.

The information derived from a simple measure of DE can help clinicians in difficult therapeutic decisions, such as escalating diuretics and/or selecting other classes of diuretics (such as mineralocorticoid receptor antagonists [27, 28]), in-hospital department allocation

(e.g., low monitoring vs. intensive monitoring ward), personalized follow-up, management expectations about disease prognosis, clinical record registries to inform future care providers (e.g., patient required high-intensity diuretic strategy or high-dose spironolactone or ultrafiltration to obtain the fluid loss goal), and it can also provide a potential endpoint for clinical trials [29, 30].

In addition, our study provides a cutoff of 140 mL/40 mg of furosemide below which DE is likely to be unsatisfactory. This is very useful and easily calculated in clinical practice. For example, 40 mg of furosemide = 1, 80 mg = 2, 120 mg = 3, and so on. Thus, a patient with 300 mL of diuresis in 3 h who received 120 mg of furosemide in the same time period has a DE of 100, i.e., a low DE, and should be monitored accordingly.

Limitations

Several limitations should be noticed in this study. First, this is a single-center, retrospective study with potential bias regarding patient selection and information registration potentially affecting the external validity of the results. Specifically, we had no information regarding some drug dosages, including nitrates. Still, these data are consistent with the findings described by Testani et al. [11] and confirm the potential of DE in a daily clinical practice cohort. Second, diuresis and diuretic dose determination were prone to errors, since the information was obtained from ER registries, which were done under stressful conditions. In addition, out-of-hospital urine output and/or diuretic dose may have not been correctly estimated – this is true for patients with a high urine output and/or a low IV furosemide dose. However, patients with a low diuresis and/or a high diuretic dose are likely to be correctly identified in this cohort, since these measures reflected the cumulative of the first 3 h after an ADHF episode. In other words, the potential for diuresis underestimation before hospital arrival is not likely to be systematic and, if present, decreases the strength of the association between the exposition and outcome. Hence, without this information bias, we would probably have estimated stronger associations. Third, the cumulative 3 h measures may not reflect the entire 3 h for all cases, since some patients may have left the ER sooner and were lost to these precise registries (from these retrospective registries, it was not possible to determine the exact time patients left the ER). Moreover, a "clinical congestion score" is not possible to estimate, since many data regarding clinical congestion were lacking and/or were not precise. Nonetheless, we used NT-pro BNP "drop" during hospitalization as a surrogate marker for effective decongestion, but even in this case a high proportion of missing values was observed, adding further limitation to the precision of these results. Fourth, diuretic resistance is relevant in patients with volume overload, and many patients here admitted for ADHF may actually have fluid redistribution/acute pulmonary edema that may not require a high DE to obtain their congestion relief goals. This can lead to an underrepresentation of patients more likely to have diuretic resistance (e.g., those with right ventricular dysfunction who tend to be more diuretic resistant and less likely to have pulmonary edema). In this regard, patients admitted in this study represent only ADHF with acute pulmonary edema/respiratory insufficiency (mostly $Pa0_2/FIO_2$ <200) and without acute myocardial infarction. Of note, the findings described in this study are derived from a "real-world" cohort of ADHF patients who entered the ER of a tertiary hospital with respiratory insufficiency (without hypotension or acute myocardial infarction). Hence, the management of these patients reflects the daily clinical practice with this portion of high-risk ADHF patients. Hence, these results can only be generalizable to patients with similar characteristics to those presented in this cohort. Fifth, the low number of patients/events affects the precision of the estimations of effects and may partly account for the loss of statistical significance in the NT-pro BNP adjustment and subgroup analysis (type II error). Sixth, oral diuretics taken before attending the ER

were not registered, and these could have decrease the need for IV diuretics, but once again this does not change the estimation of the patients with the lowest DE. Lastly, although these data derive from an unselected cohort of ADHF patients are consistent with the findings of Testani et al. [11], they should be interpreted as hypothesis generating and require validation in other cohorts.

Conclusion

A low DE (≤140 mL/40 mg of furosemide) in the first 3 h after an ADHF episode was associated with increased mid-term mortality rates. Neither diuresis nor diuretic doses alone showed significant associations with the outcome. Additional research is required to validate these findings in other ADHF cohorts and to assess if early DE can be used to tailor diuretic strategies in the management of ADHF.

Statement of Ethics

Subjects have given their informed written consent, and the study protocol was approved by the local ethics committee.

Disclosure Statement

Dr. Girerd has received board membership fees from Novartis. Dr. Rossignol has received board membership fees from Novartis, Relypsa, and Steathpeptides. Dr. Zannad has received fees for serving on the board of Boston Scientific; consulting fees from Novartis, Takeda, AstraZeneca, Boehringer Ingelheim, GE Healthcare, Relypsa, Servier, Boston Scientific, Bayer, Johnson & Johnson, and Resmed; and speaking fees from Pfizer and AstraZeneca. He and Dr. Rossignol are CardioRenal diagnosticS co-founders. Dr. Ferreira has received board membership fees from Novartis. All other authors report that they have no relationships relevant to the contents of this paper to disclose.

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