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Prognostic Implications of Diuretic Dose in Chronic Heart Failure

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Abstract

Background: Prognostic implications of diuretics dose are not completely understood. We aim to study the association between diuretic doses and long-term prognosis in patients with chronic stable heart failure (HF). **Methods and Results:** We conducted a retrospective cohort study of 244 patients followed at an outpatient HF clinic. Admission criteria were clinical stability in the previous 3 months and optimized medical therapy. Demographic characteristics, clinical, and laboratory parameters were recorded. Patients were followed for 2 years and the outcome was defined as all-cause death or hospital admission due to HF worsening. Patients on ≤80 mg furosemide were compared with those on higher doses. Patients were grouped according to furosemide dose (≤80 mg and >80 mg/d) and according to volemia as assessed by the sodium retention score: <3 (euvolemia) versus ≥3 (hypervolemia). Patients on higher diuretic doses (n = 79) were older, more hypervolemic, and more symptomatic. Patients on >80 mg furosemide had a higher risk of death or hospital admission (hazard ratio [HR]: 2.07, 95% confidence interval [CI]: 1.37-3.1). For each 40-mg furosemide tablet, there was a 67% increase in risk of an adverse outcome within 2 years. The increase in risk was independent of other variables crudely associated with prognosis. Among euvolemic patients, those on ≤80 mg/d furosemide performed better than those on higher doses. Among hypervolemic patients, the diuretic dose had no prognostic implications. **Conclusions:** Higher diuretic doses associated strongly and independently with adverse long-term outcome in chronic HF. Possibly, in euvolemic patients, efforts should be made to reduce diuretic dose.

Keywords

heart failure, diuretics, volemia, prognosis

Introduction

Diuretics have long played a role in the management of heart failure (HF) and still do.[1,2] Clinicians are well aware of the symptomatic relief these drugs can provide in the acute HF setting, and diuretics are part of the HF long-term management being recommended if there are clinical signs or symptoms of congestion.[3] However, in contrast to angiotensin-converting enzyme inhibitors (ACEIs), β-blockers (BB), and aldosterone antagonists, which have proven advantages in patient survival in large randomized controlled trials,[4-6] large prospective studies regarding the prognostic effect of diuretic use and dose on mortality are lacking.[7,8] A meta-analysis[9] of small randomized controlled trials reached the conclusion that diuretic use was associated with reduced mortality and worsening HF. Other observational and retrospective studies reported increased mortality and admission due to worsening HF for patients on diuretic therapy.[10,11] Although part of the approved HF treatment, no data exist to guide dosing strategies. Recent retrospective studies[12-15] have approached this unsolved question and reported an increased morbidity and mortality with higher diuretic use even after adjustment for baseline variables. A prospective study on 186 patients with HF found that the relation of higher loop diuretic dose with death or worsening HF admission was attenuated once clinical instability history was accounted for.[16]

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Animal studies showed a significantly faster deterioration of left ventricular systolic function and increasing serum aldosterone levels in animals receiving diuretics in comparison with placebo.[17]

In clinical practice, physicians tend to assume that patients on higher diuretic doses are more severely ill than those on a lower dose. In fact, it seems intuitive that patients needing higher diuretic doses to prevent fluid retention and control symptoms are sicker than the others. However, the potential prognostic importance of the diuretic dose in chronic HF is not well understood and, in theory, outcomes can be worsened by known diuretic side effects.

The aim of this study was to compare the profile of patients with HF according to diuretic dose and to assess the prognostic value of diuretic dose in outpatients with mild-to-moderate chronic HF.

Methods

We conducted a retrospective cohort study on ambulatory patients attending a specialized HF clinic at Hospital S. João, a public tertiary care academic hospital. Patients' medical records were screened in order to identify eligible patients. The files were screened sequentially based on the file number order; this is, from the first to the last patient referred to the HF clinic. All patients meeting the inclusion criteria were included in the study. Inclusion criteria were clinical stability in the previous 3 months on optimized medical therapy. Therapy was considered optimized when patients were on the highest tolerated doses of prognosis-modifying drugs, whenever these were indicated. Also, no change in diuretic doses was allowed in the previous 3 months. Patients with incomplete medical records and no echocardiographic evaluation were excluded. A total of 244 patients were included. Demographic and physical examination data, comorbidities, medication in use, and laboratory parameters were abstracted by 3 physicians who work at the clinic.

The diagnosis of HF was based on the European Society of Cardiology criteria.[3] As a general reference, severe left ventricular systolic dysfunction (LVSD) corresponds to left ventricular ejection fraction (LVEF) lower than 30%, moderate LVSD to LVEF between 30% and 40%, and mild LVSD to LVEF between 40% and 50%. Left ventricular ejection fraction above 50% is assumed as normal systolic function

Arterial hypertension was defined as previous medical diagnosis or pharmacological treatment, and diabetes mellitus as either a history of diabetes or the current prescription of either an oral hypoglycemic drug or insulin.

β-blocker doses presented are carvedilol equivalent doses (50 mg carvedilol = 10 mg bisoprolol = 10 mg nebivolol = 200 mg metoprolol) and ACEI doses are lisinopril equivalent (20 mg lisinopril = 8 mg perindopril = 10 mg enalapril = 20 mg fosinopril = 4 mg trandolapril = 5 mg ramipril = 150 mg captopril).

In the analysis of prognosis, we used a combined end point of all-cause death or hospital admission due to worsening HF. Length of follow-up was considered from the date of optimized therapy for 3 months until the occurrence of the end point or the last contact with the patient, censored at 2 years.

A cutoff of 80 mg of furosemide per day was used to define high and low loop diuretic dose and the few patients not on diuretics were included in the low-dose group. This cutoff was already used previously[13] and corresponded to the median value of the loop diuretic dose. We defined hypervolemia as a sodium retention score ≥ 3.[18] Patients were cross-classified according to these 2 criteria, defining 4 groups: (1) euvolemic on low diuretic dose; (2) euvolemic on high diuretic dose; (3) hypervolemic on low diuretic dose; and (4) hypervolemic on high diuretic dose.

Statistical Analysis

Continuous variables are presented as mean (standard deviation) or median (interquartile range) if nonnormally distributed. Categorical variables are presented as counts and proportions. Comparisons between groups of patients on high and low diuretic dose were made by use of a chi-square test for categorical variables, independent samples t test for continuous variables that were normally distributed, and Mann-Whitney test for continuous variables with a skewed distribution. For comparisons of a nonnormally distributed variable between more than 2 groups, a Kruskal-Wallis test was used. Survival according to diuretic dose was assessed using the Kaplan-Meier method. Cox regression analysis was used to identify variables associated with a worse outcome. All variables found to be associated with outcome in univariate analysis as well as those shown to be significantly different between low- and high-dose diuretic groups were considered in a multivariate Cox-regression model. All analyses were conducted using the Statistical Package for the Social Sciences (SPSS) 13.0 (SPSS Inc, Chicago, Illinois). A P value of $< .05$ was considered statistically significant.

Results

The baseline characteristics of the study sample are shown in Table 1. Overall, the mean age was 68 years and there was a predominance of men. The majority of patients (76.9%) had systolic HF. In all, 224 (91.8%) patients were in New York Heart Association (NYHA) class I or II. Only 15 (6.1%) patients were not taking loop diuretics.

Among the 244 study patients, 165 (67.6%) were on a low diuretic dose (furosemide $\leq$80 mg/day) and 79 (32.4%) on a higher dose. The characteristics of patients on high and low diuretic dose were compared (Table 1). Patients on >80 mg of furosemide per day were significantly older, had higher body mass index (BMI), were in higher NYHA class, were more often hypervolemic, and had worse renal function. The combined end point occurred in 48 (29.1%) patients on low furosemide dose and in 42 (53.2%) patients on high diuretic dose ($P < .001$).

Figure 1 (left panel) represents 3 box plots that compare furosemide dose according to NYHA class at baseline. Loop

Table 1. Baseline Characteristics of the Overall Study Sample and According to Diuretic Dose

	All Patients (n = 244)	Furosemide ≤80 mg/day (n = 165)	Furosemide >80 mg/day (n = 79)	*P* Value
Demographic and clinical characteristics				
Age (years), mean (SD)	68 (12)	66 (12)	72 (10)	<.001
Male gender, n (%)	163 (66.8)	115 (69.7)	48 (60.8)	.21
BMI (kg/m^2), median (IQR)	26.6 (23.4-29.4)	25.7 (22.7-28.8)	28.3 (24.5-31.4)	.001
Arterial hypertension, n (%)	155 (63.5)	99 (60.0)	56 (70.9)	.13
Diabetes mellitus, n (%)	65 (26.6)	42 (25.5)	23 (29.1)	.65
LVSF, n (%)				
Preserved	57 (23.5)	40 (24.4)	17 (21.5)	.63
Mildly depressed	36 (14.5)	25 (15.2)	11 (13.9)	
Moderately depressed	59 (24.3)	38 (23.2)	21 (26.6)	
Severely depressed	91 (37.4)	61 (37.2)	30 (38.0)	
Ischemic etiology, n (%)	102 (42.9)	64 (39.8)	38 (49.4)	.21
NYHA class, n (%)				
I-II	224 (91.8)	156 (94.5)	68 (86.1)	.04
III	20 (8.2)	9 (5.5)	11 (13.9)	
Sodium retention score, median (IQR)	1 (0-2)	1 (0-2)	2 (1-3)	<.001
Systolic blood pressure (mm Hg) median (IQR)	130 (110-146)	130 (110-146)	128 (110-140)	.33
Diastolic blood pressure (mm Hg) median (IQR)	74 (64-80)	76 (70-84)	70 (60-80)	.06
Heart rate (/min), median (IQR)	76 (68-84)	80 (68-85)	75 (68-80)	.68
Hemoglobin (g/dL), mean (SD)	13.6 (1.7)	13.6 (1.8)	13.5 (1.5)	.50
Plasma creatinine (mg/dL), median (IQR)	1.09 (0.94-1.30)	1.04 (0.93-1.23)	1.11 (0.95-1.44)	.03
Serum sodium (mEq/L), median (IQR)	141 (139-143)	140 (138-142)	141 (139-144)	.06
Medications in use				
β-blocker, n (%)	191 (78.3)	130 (78.8)	61 (77.2)	.91
Dose (mg/d), median (IQR)	25 (6.25-50)	25 (6.25-50)	25 (3.125-50)	.26
ACEI, n (%)	227 (93.0)	152 (92.1)	75 (94.9)	.59
Dose (mg/d), median (IQR)	20 (10-20)	20 (10-20)	10 (10-20)	.06
Spironolactone, n (%)	95 (39.3)	59 (36.2)	36 (45.6)	.21
Digoxin, n (%)	63 (25.8)	41 (24.8)	22 (27.8)	.73
Events, n (%)	90 (36.9)	48 (29.1)	42 (53.2)	<.001

NOTE: ACEI = angiotensin-converting enzyme inhibitor; BMI = body mass index; IQR = interquartile range; LVSF = left ventricular systolic function; NYHA = New York Heart Association; SD = standard deviation.

diuretic dose increased with increasing severity of symptoms as assessed by NYHA class. Median (interquartile range) furosemide dose was 60 (40-80) mg/d in 79 NYHA I class patients, 80 (40-120) mg/d in 145 NYHA class II patients, and 100 (80-150) mg/d in 20 NYHA class III patients ($P < .001$). At the right panel, 4 box plots are depicted that represent the furosemide dose according to left ventricular dysfunction. No difference was detected between patients with systolic and diastolic HF and loop diuretic dose was not associated with left ventricular function. Median (interquartile range) furosemide dose was 80 (40-120) mg/d in 57 patients with normal left ventricular systolic function, 80 (40-100) mg/d in 36 patients with mild LVSD, 80 (40-120) mg/d in 59 with moderate LVSD, and 80 (40-120) mg/d in 91 patients with severe LVSD ($P = .85$).

Table 2 represents the Cox univariate analysis of the association between each variable and all-cause death or HF hospital admission within 2 years. Variables crudely associated with the outcome of the study were diabetes mellitus, ischemic etiology of HF, sodium retention index, BB dose, and loop diuretic dose.

The multivariate model used is shown in Table 3. Loop diuretic dose retained its association with worse outcome, after adjustment to all other predictors—hazard ratio (HR) = 1.67; 95% confidence interval (CI): 1.28-2.16; $P < .001$.

A total of 141 (57.8%) patients were euvolemic and on a low diuretic dose; 23 (9.4%) patients were hypervolemic on a low diuretic dose, 29 (11.9%) patients were hypervolemic on a high diuretic dose, and 50 (20.5%) patients were euvolemic on a high diuretic dose, no data on sodium retention score were available in 1 study patient. Figure 2 represents a Kaplan-Meier hospitalization-free survival curve according to the 4 groups created. Euvolemic patients on high diuretic dose had a worse outcome than those who were euvolemic and on a low diuretic dose (HR [95% CI]: 2.70 [1.67-4.36]). In hypervolemic patients, diuretic dose had no prognostic value (HR [95% CI]: 1.06 [0.45-2.52]).

Discussion

Our study showed that, in a group of patients with mild-to-moderate chronic HF, the diuretic dose was associated with prognosis, especially in euvolemic patients. Higher furosemide dose was associated with higher morbidity and mortality even

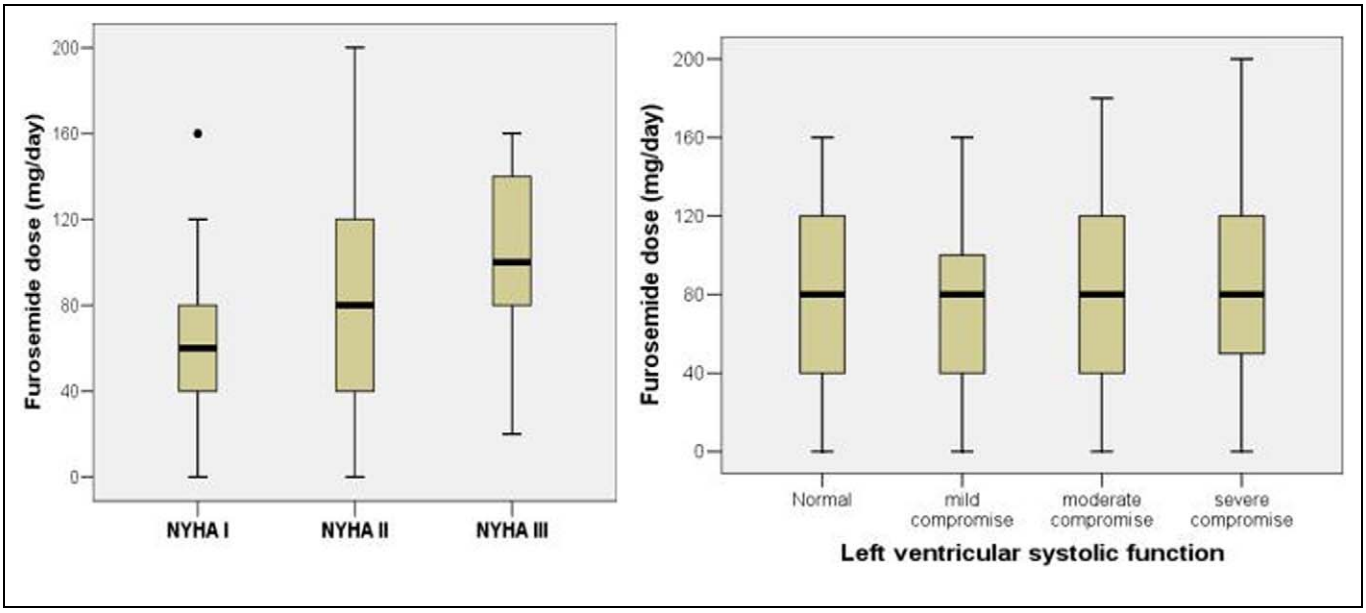

Figure 1. Left: Depicted are 3 box plots that show loop diuretic dose distribution according to NYHA class. Furosemide dose increased with increasing severity as assessed by NYHA class, $P < .001$; Right: Depicted are 4 box plots that represent the loop diuretic dose according to left ventricular dysfunction. No difference was detected between patients with systolic and diastolic HF and furosemide dose did not associate with HF severity as assessed by left ventricular function, $P = .85$. HF indicates heart failure; NYHA, New York Heart Association.

after adjustment for other predictors of adverse outcome, namely hypervolemia assessed in accordance to the sodium retention score. For each furosemide tablet on top of an otherwise optimized medical therapy, there was a 66% (95% CI: 28-116) increase in the risk of all-cause death or hospitalization due to worsening HF within 2 years.

Several mechanisms[18-21] have been suggested to interpret the apparent deleterious effects of diuretic therapy and to support the possibility of a causality relation between high diuretic doses and poor clinical outcome. Renin-angiotensin-aldosterone axis[22-26] and sympathetic nervous system[26] activation; volume depletion, hypotension, and renal dysfunction[27]; and electrolytic disturbances[28,29] are deleterious effects of diuretic agents that may actively participate in the progression and clinical deterioration of patients with HF. Increasing myocardial fibrosis associated with diuretic use[30,31] and diuretic resistance[32] have also been described. Special emphasis has been given to potassium and magnesium depletion, since deficit of these ions relates with increased risk of arrhythmic events as well as with increased vasoconstriction.[33] Neurohormonal axis activation can act as a feed-forward mechanism as it aggravates vasoconstriction and additionally reduces blood flow to the kidney. In this context, diuretic resistance can be interpreted as the diminished capacity of the organism to deliver the same amount of diuretic to act on the kidney because of a reduced perfusion.[34] Higher dosages are thus needed to obtain the same effect that lower doses produced before.

We included in our study the assessment of volemia as it may interfere with both the diuretic dose needed and the physician's perception of HF severity. Even though the use of >80 mg furosemide per day was associated with worse NYHA class, it was also true that many patients on high loop diuretic dose were euvolemic. Thus, in contrast with previous studies, we created groups according to these 2 characteristics and we verified that there was a substantial difference between euvolemic patients on low and on high furosemide dose when outcome was considered. Euvolemic patients on higher diuretic dose had an almost 3-fold increase in the risk of death or readmission (2.70, 95% CI: 1.67-4.36) in comparison with euvolemic patients on lower doses ($\leq$80 mg/d). Hypervolemic patients whether on high or on low diuretic dose represent a gray zone, performing not significantly better than euvolemics on high diuretic dose nor significantly worse than euvolemics on low diuretic dose.

For assessment of congestion, we used the sodium retention score proposed by Cody, which was the first described in the literature.[18] The need for a quantification of volume overload is still recognized and underscored nowadays.[35] A complex congestion score[36] that gathers information from bedside assessment, laboratory measurements, and dynamic maneuvers was recently described, but it is not feasible to enter everyday clinical practice. The score proposed by Cody[18] has the advantage of being simple and based only on bedside assessment parameters that have all shown to correlate with left-hand or right-hand side congestion, and it has been suggested that their combination would increase their predictive value.[36]

The prognostic implications of loop diuretic dose showed a linear effect—patients had progressive outcome deterioration per each furosemide tablet increase. This linear relation and the independent association with outcome in a multivariate model suggest that loop diuretics may have an intrinsic deleterious effect.

Table 2. Cox Univariate Analysis of Candidate Predictors of Prognosis

	HR (95% CI)
Demographic and clinical characteristics	
Age (per year)	1.01 (0.99-1.03)
Male gender	1.34 (0.84-2.12)
BMI (per kg/m^2)	1.00 (0.98-1.01)
Arterial hypertension	1.13 (0.73-1.74)
Diabetes mellitus	1.73 (1.12-2.68)
Systolic HF	1.49 (0.89-2.50)
Severe LVSD	1.38 (0.91-2.09)
Ischemic etiology	1.55 (1.02-2.36)
NYHA class III (vs II/I)	1.40 (0.70-2.78)
Sodium retention index (per unit)	1.16 (1.01-1.33)
Systolic blood pressure (per mm Hg)	1.00 (0.99-1.00)
Diastolic blood pressure (per mm Hg)	0.98 (0.96-0.99)
Heart rate (per min)	1.00 (0.98-1.02)
Hemoglobin (per g/dL)	0.95 (0.84-1.08)
Plasma creatinine (per mg/dL)	1.20 (0.74-1.95)
Serum sodium (per mEq/L)	0.98 (0.92-1.04)
Medications in use	
Beta-blocker (yes vs no)	0.87 (0.54-1.41)
Beta-blocker dose (per mg of carvedilol/day)	0.99 (0.98-1.00)
ACE-inhibitor (yes vs no)	1.84 (0.68-5.02)
ACE-inhibitor dose (per mg of lisinopril/d)	0.98 (0.96-1.01)
Spironolactone	0.85 (0.55-1.32)
Digoxin	1.21 (0.77-1.90)
Furosemide (above vs below 80 mg/d)	2.07 (1.37-3.14)
Furosemide (per 40 mg/d)	1.51 (1.23-1.86)

NOTE: ACEI = angiotensin-converting enzyme inhibitor; BMI = body mass index; CI = confidence interval; HF = heart failure; HR = hazard ratio; LVSD = left ventricular systolic dysfunction; NYHA = New York Heart Association.

Table 3. Multivariate Cox-Regression Model[a]

	Hazard Ratio	95% Confidence Interval	*P* Value
Furosemide (per 40 mg/d)	1.67	1.28-2.16	<.001
β-blocker dose (per mg/day)	0.99	0.98-1.00	.03
Diabetes mellitus	2.01	1.24-3.25	.005
Diastolic blood pressure (per mm Hg)	0.98	0.96-1.00	.04
Age (per year)	0.98	0.96-1.00	.06
Sodium retention index (per unit)	0.98	0.84-1.15	.81
NYHA class III (vs II/I)	0.63	0.28-1.44	.28
BMI (per kg/m^2)	0.97	0.92-1.03	.32
Plasma creatinine (per mg/dL)	0.82	0.46-1.45	.49
Ischemic etiology of HF	1.00	0.88-1.14	1.00
ACEI dose (per mg/d)	0.99	0.96-1.01	.40

NOTE: ACEI = angiotensin-converting enzyme inhibitor; BMI = body mass index; NYHA = New York Heart Association.

[a] Variables crudely associated with the combined end point as well as variables shown to be different in high- and low-dose loop diuretic groups entered the model.

Our results reinforce the empiric strategy of down-titration of diuretic dose once symptomatic control and euvolemia are achieved. This could be managed, like insulin adjustments for diabetics, by a patient-controlled protocol, in which patients would titrate their diuretic dose according to symptom severity.[37]

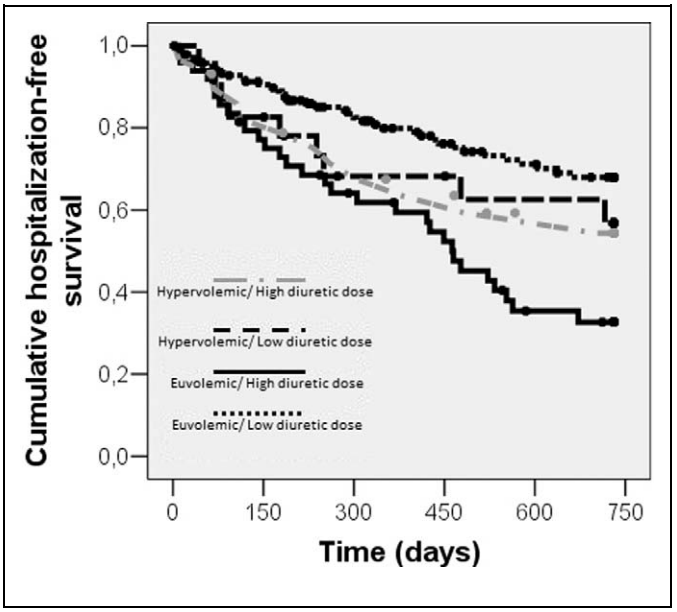

Figure 2. Kaplan-Meier hospitalization-free survival curve according to the 4 groups created: euvolemic patients on high furosemide dose; euvolemic patients on low furosemide dose; hypervolemic patients on high diuretic dose; and hypervolemic patients on low diuretic dose Euvolemic patients on high diuretic dose showed significantly worse cumulative hospitalization-free survival than those who were euvolemic and on a low diuretic dose. Hypervolemic patients represent a gray zone.

Our study has several limitations. It is a retrospective single-centered study. The retrospective nature of the study precluded definite conclusions about cause–effect relations and prognostic implications of the variables in this study. Also, we did not take into consideration the possible changes in diuretic dose and volemia status over time. A single baseline evaluation is not enough and does not eliminate the great potential of confounding by indication. Another important setback of this study is the lack of data on natriuretic response, since urine analyses were not available for most patients. Important variables that we cannot exclude to have had prognostic implications were serum magnesium (measure of ion depletion) and plasma renin activity as well as serum aldosterone determination (measure of neurohumoral-activation). Since there was a trend for patients on higher diuretic doses to be on lower ACEI doses, we cannot exclude that the worse outcome of those on >80 mg furosemide per day was at least in part due to the suboptimal doses of ACEIs. However, the prognostic impact of the diuretic dose was independent of the ACEI dose. Despite all these limitations, a relatively large sample of patients and a long time of follow-up were considered. Most patients were in NYHA class I and II, precluding extrapolation of the results to a more symptomatic patient population. We cannot accurately predict the results that would be observed in such patients, but considering that patients in higher classes were more often hypervolemic, we expect that diuretic dose would have a weaker prognostic impact or none whatsoever in this subgroup.

Differently from other studies, the sodium retention score was used to assess the volemia and to create 4 groups according to the diuretic dose and the presence of hypervolemia. The retrospective nature of the study, with all its inherent problems, has however the potential benefits of not influencing the prescription patterns.

The question that the study tries to address represents an example of the rare situations in which a retrospective design can overcome the bias of the influence of the study itself on prescription; one such bias would be very difficult to control in a prospective design.

Conclusions

Higher diuretic dose is independently associated with worse outcome. Our results suggest that, especially in patients with euvolemic HF, efforts to reduce the diuretic dose might be beneficial. Additional studies have to be conducted to support this hypothesis.

Declaration of Conflicting Interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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