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Clinical Investigation

Prognostic Effect of the Dose of Loop Diuretic Over 5 Years in Chronic Heart Failure

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ABSTRACT

Background: High diuretic doses in chronic heart failure (HF) are potentially deleterious. We assessed the effect of dynamic furosemide dose on all-cause mortality among HF ambulatory patients.

Methods and Results: A cohort of 560 ambulatory patients from an outpatient clinic specialized in HF, with median age 70 years, 67% male, and 89% with moderate-severely reduced ejection fraction, was retrospectively followed for up to 5 years. Dynamic furosamide exposure was categorized as low (0–59 mg/d), medium (60–119 mg/d), high (120–159 mg/d), and very high (≥160 mg/d). Extended Cox models were used to estimate the association between time-varying diuretic dose and mortality. A dose-dependent crude association between higher doses of furosemide and death (hazard ratio [HR] = 1.34, 95% confidence interval (CI): 1.06–2.16; HR = 2.09, 95% CI: 1.54–2.84, for high and very high dose, respectively) was totally explained by patients' characteristics and disease severity indicators (adjusted HR = 0.94, 95% CI: 0.63–1.38; HR = 1.10, 95% CI: 0.79–1.55, for high and very high dose, respectively).

Conclusion: In this context, higher doses of diuretic did not impair survival, but rather indicated greater severity of the patient's condition. (*J Cardiac Fail 2017;23:589–593*)

Key Words: Heart failure, loop diuretics, dose, prognosis.

Congestion is a key component of heart failure (HF) that determines symptoms, hospital admissions, and mortality.[1] Of all drugs used in HF, diuretics are the most efficacious for relief from fluid congestion,[2] thus becoming the most frequently prescribed drug class[3] despite the limited evidence to guide their prescription and titration. The use of inappropriately low doses of diuretics may lead to persistent edema, whereas high doses may result in volume contraction, which can increase the risk of hypotension and renal insufficiency.[4]

According to guidelines, the aim of using diuretics is to achieve and maintain a euvolemic state and patients' well-being with the lowest achievable dose.[5] This requires individual diuretic dose adjustments given the progressive character of HF, its concomitant conditions and treatments, and changes in dietary sodium and fluid intake over time. In this study, we assess the association of the fluctuating dose of furosemide with all-cause mortality over 5 years in ambulatory patients within a wide spectrum of HF presentation.

Methods

For this retrospective cohort study, we screened 765 consecutive ambulatory patients referred between January 2000 and July 2011 to the HF clinic at Hospital São João in Porto, Portugal. Inclusion criteria of HF diagnosis[5] and reduced ejection fraction (≤50%) were confirmed in 632 patients; those with uncorrected primary valvular disease (n = 10), on dialysis (n = 4), and attending only 1 appointment at the clinic (n = 58) were excluded, leaving 560 patients for analysis.

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Data on patients' characteristics, prescribed therapy, and laboratory parameters were abstracted from records of each clinical appointment during the study period, corresponding to 4978 observations. Dynamic diuretic exposure was determined based on furosemide dose prescribed at each medical visit. After consultation with cardiologists specialized in HF, the daily dose was categorized as low (0–59 mg), medium (60–119 mg), high (120–159 mg), and very high doses (≥160 mg). Qualitative assessment of left ventricular ejection fraction was considered as documented in clinical records. N-terminal prohormone of brain natriuretic peptide (BNP) values were converted into BNP[6] and serum sodium ≤133 mEq/L was defined as moderate or severe hyponatremia.[7]

Patients were followed until July 31, 2012, for the endpoint of all-cause mortality. Vital status was ascertained using the clinic's records and telephone contacts. Patients were censored if regular hemodialysis was instituted, there was no appointment at the clinic for more than 15 months, or after 5 years after referral, whichever came first. The study was approved by the institutional ethics committee.

Statistical Analysis

Baseline dose categories were compared using the $\chi 2$ test for discrete and 1-way analysis of variance or Kruskal-Wallis tests for continuous variables. Survival was estimated using the Kaplan-Meier method. Forty-five percent of observations had no data on at least 1 laboratory parameter, to a large extent representing no need for tests in stable patients. Data on variables other than laboratory parameters were lacking in 6% of observations. Absent and missing data, as well as nonexistent BNP values (N-terminal prohormone of BNP/BNP blood test became available at the hospital after 2003) were handled by multiple imputation using mixed effects multivariable regression models. Extended Cox models were used to assess the association between dynamic diuretic dose and all-cause mortality. The dynamic dose was sequentially adjusted for the baseline dose (Table 1, model 2), time-independent confounders (age, sex, ischemic etiology, diabetes mellitus, and atrial fibrillation) (model 3), time-varying disease severity indicators (hospital admissions resulting from HF, New York Heart Association [NYHA] class, and BNP) (model 4), time-varying laboratory and physiologic parameters (creatinine, sodium, and systolic blood pressure), (model 5) and concomitant disease-modifying treatments (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and β-blockers) (model 6).

Sensitivity analyses were performed to examine the effect of increased dose of furosemide on 2-year survival. Statistical analyses were performed using Stata and R softwares. P values <.05 were considered significant.

Results

Overall characteristics at referral included median age of 70 years, 67% male, 46% of ischemic etiology, 89% with moderate-severely reduced EF, and 62% in NYHA class II (Table 2).

Higher referral daily diuretic doses were related with clinical markers of more severe disease, including higher NYHA class, higher BNP and serum creatinine, lower systolic blood pressure, and lower hemoglobin levels. Patients on higher daily diuretic doses were more often hospitalized for HF in the preceding year and more frequently had comorbidities. Over 6 months and 5 years of follow-up, 85% and 40% of patients remained in the same diuretic dose category as at baseline, respectively (Fig. 1).There were 109 deaths during the follow-up period, with increasing 5-year risk of death across referral diuretic dose categories (26%, 32%, 43%, and 56% in low, medium, high, and very high dose groups, respectively; log-rank test: $P < .001$).

In univariable analysis of dynamic dose (Table 1, model 1) a higher furosemide dose was associated with a progressively higher mortality. When adjusted for baseline dose (model 2) and other time-independent confounders (model 3), very high dose was independently related with higher risk of death; however, this association became close to null after controlling for HF severity (model 4). Subsequent adjustment for serum creatinine, systolic blood pressure, and hyponatremia (model 5), and additionally for prognosis-modifying therapy (model 6), had no impact on the association between diuretic dose and risk of death.

In sensitivity analysis, high furosemide dose prescribed at referral was associated with higher 2-year mortality, whereas

Table 1. Hazard ratio for mortality according to time-varying diuretic dose categories over 5 years, adjusted for the baseline dose and multiple confounders

Model	Low	Medium	High	Very High	Variables Included
1	1*	1.38 (1.00–1.89)	1.51 (1.06–2.16)†	2.09 (1.54–2.84)†	Time-varying diuretic dose
2	1*	1.28 (0.93–1.77)	1.34 (0.93–1.93)	1.85 (1.36–2.53)†	Baseline diuretic dose + time-varying diuretic dose
3	1*	1.18 (0.86–1.61)	1.22 (0.85–1.76)	1.63 (1.19–2.22)†	Model 2 + age + sex + ischemic etiology + atrial fibrillation + diabetes mellitus (baseline)
4	1*	1.06 (0.76–1.45)	0.94 (0.65–1.37)	1.06 (0.76–1.47)	Model 3 + NYHA class + BNP + HF hospitalization (baseline and time-varying)
5	1*	1.08 (0.78–1.49)	0.97 (0.66–1.43)	1.12 (0.80–1.57)	Model 4 + serum creatinine + blood pressure + hyponatremia (baseline and time-varying)
6	1*	1.11 (0.80–1.54)	0.94 (0.63–1.38)	1.10 (0.79–1.55)	Model 5 + ACE inhibitor + β-blocker treatment (baseline and time-varying)

N = 560 patients; 4978 observations; absent data in each observation (missing or no laboratory tests ordered) were imputed.
*Reference class.
†$P < .05$ vs. low dose.

Table 2. Patient Characteristics at Baseline

		All	Low Dose	Medium Dose	High Dose	Very High Dose	*Pvalue*
No. of patients		560	164	252	93	51	
Age (y), median (IQR)		70.0 (57.3–78.7)	65.8 (53.7–76.5)	70.1 (57.1–79.2)	74.1 (63.5–79.7)	70.2 (61.5–77.0)	.015
Male sex, %		67.0	69.5	64.7	68.8	66.7	.748
Ischemic etiology, %		46.1	45.1	46.8	40.9	54.9	.434
Diabetes mellitus, %		35.5	32.3	34.1	37.6	49.0	.159
Hypertension, %		61.6	58.5	62.7	61.3	66.8	.720
Arial fibrillation, %		37.7	24.4	40.9	48.4	45.1	<.001
Chronic kidney disease, %		45.7	32.9	48.0	46.2	74.5	<.001
Hospitalization for HF in previous year, %		45.5	29.3	50.0	52.7	62.6	<.001
Ejection fraction (%), median (IQR)*		26 (20–35)	28 (21–35)	27 (20–35)	25 (21–33)	25 (20–30)	.304
Moderate-severe reduced EF, %		88.9	88.4	88.5	88.2	94.1	.673
NYHA class, %	I	18.7	29.2	18.5	8.0	6.0	
	II	62.0	57.8	65.4	59.8	62.0	
	III	18.0	13.0	15.2	28.7	28.0	
	IV	1.3	0.0	0.9	3.5	4.9	<.001
Systolic blood pressure (mmHg), mean (SD)		120.4 (24.3)	124.1 (24.6)	119.9 (24.7)	120.7 (23.8)	110.8 (20.1)	.012
Heart rate (beats/min), mean (SD)		78.3 (13.9)	78.5 (12.5)	78.1 (14.5)	78.6 (14.1)	78.1 (15.7)	.985
BNP (pg/mL), median (IQR)		458.5 (224.8–1047.0)	193.4 (93.8–454.2)	530.5 (263.1–995.8)	569.1 (306.7–1441.4)	1281.0 (508.1–2918.5)	<.001
Creatinine (mg/dL), median (IQR)		1.1 (0.9–1.4)	1.0 (0.9–1.3)	1.1 (1.0–1.4)	1.1 (0.9–1.5)	1.4 (1.0–2.0)	<.001
Uric acid (mg/L), median (IQR)		74.9 (62.7–89.2)	67.0 (56.4–79.2)	76.6 (64.8–90.8)	77.7 (63.4–93.9)	88.4 (70.3–110.5)	<.001
Hyponatremia, %		6.7	6.2	5.2	6.2	15.7	.057
Hemoglobin (g/dL), mean (SD)		13.2 (1.9)	13.5 (1.9)	13.2 (1.9)	12.8 (1.9)	12.5 (2.0)	.009
Diuretic dose (mg/day), median (IQR)		80 (40–120)	40 (20–40)	80 (80-80)	120 (120-120)	160 (160-160)	<.001
Metolazone, %		2.3	0.0	1.2	4.3	11.8	<.001
ACE inhibitors, %		89.8	92.1	88.9	89.3	88.2	.724
β-blocker, %†		75.4	74.4	78.6	65.6	80.4	.073
Spironolactone, %		32.5	19.5	36.1	41.0	41.2	<.001
Follow-up (months), median (IQR)		23 (9–44)	26 (10–48)	22 (10–41)	19 (8–40)	16 (6–51)	.192
Time between appointments (days), median (IQR)		79 (41–123)	94 (54–153)	83 (41–118)	62 (34–104)	62 (34–97)	<.001
No of visits/patient		8 (4–12)	8 (4–11)	8 (4–13)	7 (3–13)	8 (3–15)	.848

ACE, angiotensin–converting enzyme; BNP, brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; HF, heart failure; IQR, interquartile range; MI, myocardial infarction; NYHA, New York Heart Association; SD, standard deviation.

*Data available for 264 patients.

†Carvedilol, bisoprolol, or nebivolol.

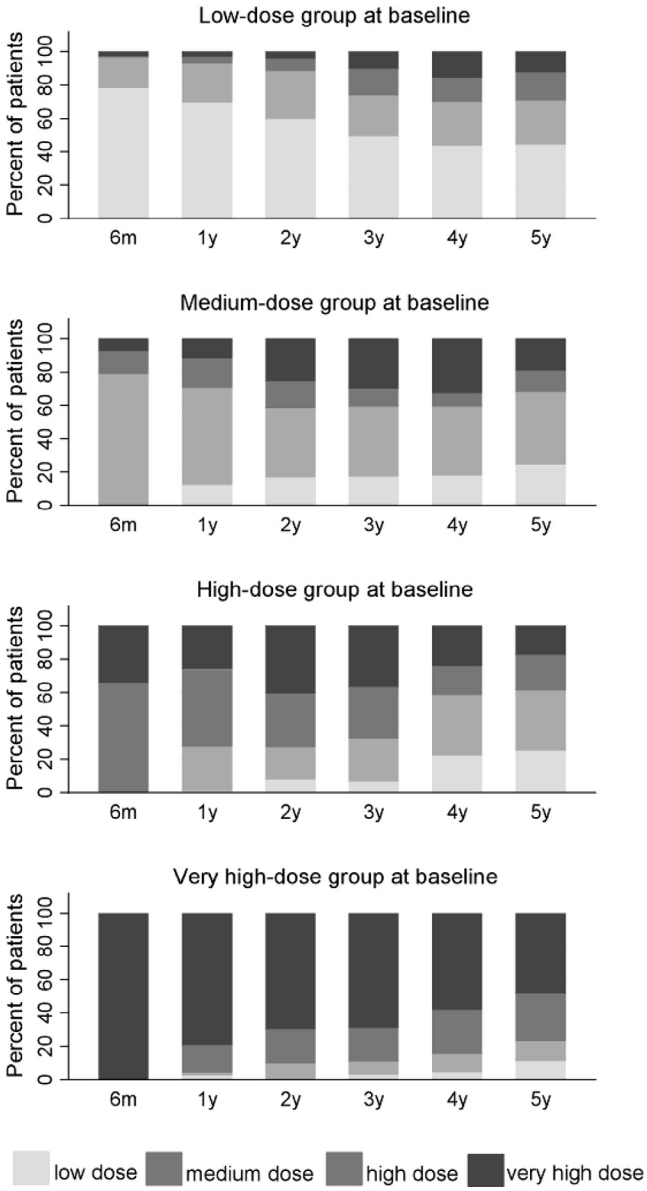

Fig. 1. Diuretic dose categories distribution over 5 years according to furosemide dose at baseline.

time-varying dose showed no effect on risk of death Appendix S1, (Supplementary Table A, model 6).

Discussion

Higher doses of furosemide were strongly associated with subsequent death, with a clear dose-dependent increase in crude risk. However, the association was totally explained by patients' characteristics and confounders reflecting the severity of the patient's condition and greater comorbidities.

Our conclusion that diuretics dose may be more a marker than a cause of instability is consistent with previous reports.[3,8] At the same time, high diuretic doses were associated with increased rehospitalizations and mortality.[9] Evaluation of the prognostic effect of diuretic in chronic therapy based on single baseline dose only may be a simplification, especially for long-term perspective. Currently, there is no specific strategy for diuretic treatment in HF, and recommendations are for the minimum dose to allow maintenance of the euvolemic state.[5] This may require a process of frequent reappraisal of diuretic regimen in the face of changes in disease status, concomitant medication, and dietary sodium and fluid intake. Adjustment of diuretic dosing according to fluid overload has been related with more favorable prognosis.[10,11] In our clinic, furosemide dose is determined during each appointment in respect to the actual volume status (presence of edema, rales, orthopnea, weight control, jugular venous pressure) and overall clinical condition (NYHA class, laboratory test), assuring that the prescribed therapy responds to the individual's demands. The need for dynamic furosemide dose analysis was reaffirmed by the frequent dose readjustments; one-half of patients altered diuretic dose within 1 year after referral, more often toward higher doses.[12] Despite widespread support for titrated diuretic dose in HF management, prognostic implication of time-varying diuretic dosage has not been thoroughly investigated. Abdel-Qadir et al[13] suggested that exposure to higher furosemide dose was associated with increased risk of hospital readmission and death; however, the effect of the dynamic dose was controlled for baseline covariates only. In our study, after multiple adjustments for time-varying factors and the risk of death were not significantly different between patients treated with low and high doses.

In a sensitivity analysis, we demonstrated that, in the medium term, the baseline diuretic dose carries a distinct prognostic value, explaining at least in part the strong association reported previously for shorter follow-up.[14,15] However, in the longer perspective, its importance decreased in favor of the time-varying dose (Appendix S1, Supplementary Table B, model 6).

The study provided detailed information on outpatient diuretic exposure over time and extensive characterization of disease severity and other potential confounders for inclusion in the time-dependent analysis in a relatively large sample of patients.

We did not consider in-hospital and postdischarge diuretic doses as well as possible influence of the patient's adherence to medications on mortality. In our clinic, furosemide is the only loop diuretic prescribed to chronic patients; a possible short course of metolazone translates into a negligible exposure time. The group of 58 excluded patients was not significantly different from the participants in baseline characteristics; therefore, a putative selection bias is expectedly small. The use of medical records of routine care contributes to the pragmatic generalizability of the results; however, findings of this single-center study may not be extrapolated to different settings.

In conclusion, ambulatory HF patients experienced frequent furosemide dose adjustment, usually toward higher doses. Intensity of diuretic treatment seems to reflect the severity of patient's condition, and its chronic use had no independent effect on 5-year survival. Our results confirm that aggressive diuretic therapy may be safe if adequately tailored for congestion status.

Disclosures

There are no conflicts of interests.

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Appendix: Supplementary Data

Supplementary data related to this article can be found at doi:10.1016/j.cardfail.2017.04.001.

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