ORIGINAL ARTICLE

The ratio of furosemide dosage to urinary sodium concentration predicts mortality in patients with chronic stable heart failure

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KEY WORDS

chronic heart failure, diuretic resistance, urinary sodium

ABSTRACT

INTRODUCTION The urinary sodium (UNa) concentration is associated with outcomes in patients with acute heart failure (HF). Its impact in individuals with chronic HF is unknown.

OBJECTIVES This study examined the combined effect of diuretic dosage and UNa concentration in chronic HF.

PATIENTS AND METHODS The research sample for this retrospective cohort study consisted of ambulatory patients receiving optimized therapy and followed in an HF clinic. The patients were recruited between 2009 and 2012. The exclusion criteria were therapeutic adjustments or hospital admissions in the previous 2 months and renal replacement therapy. The patients were followed for 5 years; the endpoint was all-cause mortality. The association between the ratio of furosemide dosage to UNa concentration and 5-year mortality was studied using a receiver operating characteristic (ROC) curve. The patients were cross-classified according to daily furosemide dosage (with the cutoff set at 80 mg) and UNa concentration (80 mEq/l). Multivariable Cox regression analysis was used to assess the prognostic impact of the ratio.

RESULTS We analyzed 283 patients with chronic HF (70.3% male; mean age, 69 years). During follow-up, 134 patients died. The median furosemide dosage was 80 mg/day and the mean UNa concentration was 85 mEq/l. Based on the ROC curve, the best cutoff for the ratio of daily furosemide dosage to UNa concentration was 0.8. Patients with a ratio of 0.8 or higher had an adjusted hazard ratio for 5-year mortality of 2.85 (95% CI, 1.78–4.58). Patients with a UNa excretion rate of less than 80 mEq/l who were administered 80 mg or more of furosemide per day were found to have a worse prognosis (HR, 4.15; 95% CI, 2.31–7.45) when compared with those with a UNa excretion rate of 80 mEq/l or more and less than 80 mg furosemide per day.

CONCLUSIONS Combining the diuretic dosage and measurement of UNa excretion can be used to refine risk stratification in chronic HF. The furosemide-to-UNa ratio can be a surrogate marker for diuretic resistance and has a prognostic impact in chronic HF.

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INTRODUCTION Diuretic resistance frequently accompanies the progression of heart failure (HF).[1,2] Congestion that is refractory to diuretic therapy portends an ominous prognosis in HF patients and, as anticipated, elevated doses of loop diuretics have been associated with poor outcomes in both acute and chronic HF.[3-6] The urine output in response to diuretic administration and the change in weight in the days following the increase of diuretic dose are indirect measures of the diuretic's efficacy.[7-9] The ability of the kidney to excrete the sodium excess, as measured by urinary sodium (UNa) concentration, has been reported to be associated with outcomes in acute

WHAT'S NEW?

The urinary sodium concentration affects the prognosis in patients with acute heart failure. In this study, we suggested that it might also play a role in chronic stable heart failure. We found that a ratio of furosemide dosage to urinary sodium concentration, which is an indirect measure of diuretic resistance, was related to outcomes in patients with chronic stable heart failure. Patients excreting more sodium with a lower diuretic dosage seem to have better survival than those excreting low sodium with a higher diuretic dosage. This ratio can be useful in stratifying patients with chronic heart failure in terms of the mortality risk and it could help determine the optimal individual diuretic dosage.

HF.[3,4,10-13] However, the significance of UNa concentration in chronic HF is largely unknown.

The disruption of sodium and fluid homeostasis with marked sodium avidity is a hallmark of HF.[14] Therefore, UNa has emerged as a potential biomarker of interest for risk stratification in patients with chronic HF, as it apparently correlates with HF severity and may reflect vulnerability to decompensation.[14,15]

Recently, metrics of diuretic responsiveness, such as net fluid loss per milligram of loop diuretic equivalent or weight loss indexed to diuretic dosage, have been suggested to provide incremental prognostic information beyond that gleaned from changes in weight, fluid balance, or loop diuretic dosage alone.[3,16] Moreover, UNa concentration may also be used to predict an acute HF admission episode in stable HF patients.[17]

Diuretic resistance is difficult to translate in easy-to-measure parameters in clinical practice. We aimed to assess the ability of an indirect measure of diuretic resistance—the ratio of furosemide dosage to UNa concentration—to predict prognosis in chronic HF patients. Additionally, we aimed to study the combined effect of both diuretic dosage and UNa concentration in this group of patients.

PATIENTS AND METHODS We retrospectively studied a cohort of chronic stable HF patients followed in an HF clinic of a tertiary care academic hospital who had been prospectively recruited between May 2009 and December 2012. Consecutive patients under optimized, evidence-based therapy according to the existing guidelines were eligible for inclusion in the study. Patients with therapeutic adjustments or hospital admissions in the previous 2 months as well as those on renal replacement therapy were excluded. On admission, all patients underwent a complete physical examination and had venous blood samples drawn. Urinary sodium concentration was measured in morning spot urine and 24-h urine samples. Demographic data, comorbidities, and medications in use were recorded. Patients with HF with a left ventricular ejection fraction (LVEF) of at least 50% were considered to have preserved ejection fraction (HFpEF), while patients with an LVEF between 40% and 49% were considered to have HF with mid-range ejection fraction (HFmrEF). Severe left ventricular systolic dysfunction corresponded to an LVEF of less than 30%; moderate systolic dysfunction corresponded to an LVEF between 30% and 39%; and together they formed the group of patients with HF with reduced ejection fraction (HFrEF).

Comorbidities were defined as follows. Diabetes mellitus was recorded when there was a known previous diagnosis or current prescription of either an oral hypoglycemic agent or insulin. Arterial hypertension was determined in cases of a previous diagnosis or a record of antihypertensive pharmacological treatment. Coronary heart disease was defined as a history of acute myocardial infarction or imaging-confirmed significant coronary heart disease.

With regard to disease-modifying drugs, their doses were presented as follows. Doses of β-blockers were presented as carvedilol equivalents: 50 mg of carvedilol equaled 10 mg of bisoprolol or 10 mg of nebivolol. Doses of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers were presented as lisinopril equivalents: 20 mg of lisinopril equaled 10 mg of perindopril, 10 mg of ramipril, 20 mg of enalapril, 16 mg of candesartan, 100 mg of losartan, 160 mg of valsartan, or 300 mg of irbesartan. All patients taking mineralocorticoid receptor antagonists were administered spironolactone.

The patients were followed for up to 5 years and the study endpoint was all-cause mortality. Vital status was ascertained by consulting hospital registries and by telephone contact with the patients or their relatives. When no information was available, we consulted the platform of the Registo Nacional de Utentes.

The ratio of furosemide dosage (mg/day) to UNa concentration (mEq/l) was used as an estimate of diuretic efficacy. The patients were classified as receiving a low (<80 mg/day) or high (≥80 mg/day) furosemide dose and as having low (<80 mEq/l) or high (≥80 mEq/l) sodium urinary excretion.

The study protocol conformed to the ethical guidelines of the declaration of Helsinki.

Statistical analysis The data were compared using the χ^2 test for categorical variables, *t* test for normally distributed continuous variables, and Mann–Whitney test for variables with a highly skewed distribution.

A receiver operating characteristic curve was used to assess the association of the furosemide dosage to UNa concentration ratio with 5-year all-cause death and Youden index was calculated in order to determine the best cut-off point for such association. Cox regression analysis was used to study the association between the variables (including this ratio) and mortality in chronic HF. A multivariable model was built using age, sex, history of hypertension or diabetes mellitus, the presence of severe systolic dysfunction, ischemic etiology of

TABLE 1 Characteristics of the study patients

Parameter		Value
Male sex		199 (70.3)
Age, y		69 (13)
History of arterial hypertension		177 (62.5)
Diabetes mellitus		105 (37.1)
Left ventricular function	HFpEF	19 (6.7)
	HFmrEF	48 (17)
	HFrEF	216 (76.3)
Ischemic etiology of HF		123 (43.5)
NYHA class	I	88 (31.1)
	II	145 (51.2)
	III	50 (17.7)
SBP, mm Hg		121 (21)
Laboratory parameters		
Hemoglobin, g/dl		13 (1.9)
Creatinine, mg/dl		1.26 (0.43)
Serum Na concentration, mEq/l		139 (3)
UNa concentration, mEq/l, median (IQR)		85 (65–106)
24-h UNa excretion, mEq		159 (74)
BNP, pg/ml, median (IQR)		236.3 (113.3–627)
Medications		
β-Blocker		270 (95.4)
β-Blocker dose, mg, median (IQR)		25 (12.5–50)
ACEI and/or ARB		262 (92.6)
ACEI and/or ARB dose, mg, median (IQR)		10 (5–20)
MRA		94 (33.2)
MRA dose, mg, median (IQR)		12.5 (12.5–25)
Furosemide		257 (90.8)
Furosemide dose, mg, median (IQR)		80 (40–120)
Thiazide diuretics		13 (4.6)
Death		134 (47.3)

Data are presented as number (percentage) or mean (SD) unless otherwise indicated.

SI conversion factors: to convert BNP to ng/l, multiply by 1.0; creatinine to μmol/l, by 88.4; hemoglobin to g/l, by 10.0, Na to mmol/l, by 1.0.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, B-type natriuretic peptide; IQR, interquartile range; MRA, mineralocorticoid receptor antagonists; 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; Na, sodium; NYHA, New York Heart Association; SBP, systolic blood pressure; UNa, urinary sodium

HF, New York Heart Association (NYHA) class, systolic blood pressure, B-type natriuretic peptide (BNP), creatinine, sodium, and hemoglobin levels, and evidence-based therapy.

Patients were additionally cross-classified according to furosemide dosage (cutoff set at 80 mg/day) and UNa excretion (cutoff set at 80 mEq/l). The Kaplan–Meier estimator was used to assess survival according to this classification. Multivariable Cox regression analysis was performed; adjustments were made for age, history of hypertension or diabetes mellitus, ischemic etiology of HF, NYHA class, systolic blood pressure, BNP, creatinine, sodium, and hemoglobin levels, and evidence-based therapy.

For both multivariable models, the variables considered for adjustment were all those which were differently distributed between patients receiving high or low furosemide doses or between patients with high or low UNa excretion rates and prognostically associated in the univariable approach.

The Kaplan–Meier method was used to plot the survival curves according to the groups created, whether based on the ratio of furosemide dosage to UNa concentration, high/low furosemide dosage, or UNa excretion.

The *P* value considered for statistical significance was 0.05. The data were stored and analyzed using SPSS software, version 20.0 (IBM, Armonk, New York, United States).

RESULTS We studied 283 chronic stable HF patients, of which 199 (70.3%) were male; the mean age was 69 years. The majority of the patients (76%) had HFrEF (58% presented severe systolic dysfunction), while 17% had mild systolic dysfunction/HFmrEF, and 7% had HFpEF. The median (interquartile range) furosemide dosage in use was 80 mg/day and the mean (SD) UNa concentration was 85 (30) mEq/l. The median (interquartile range) furosemide to UNa ratio was 0.89 (0.45–1.45). During follow-up, 134 patients (47.3%) died. The characteristics of the patients are shown in **TABLE 1**.

Patients receiving high furosemide doses (≥80 mg/day) more often had diabetes, severe systolic dysfunction, and a higher NYHA class; they also had lower hemoglobin levels, worse renal function, higher BNP levels, and lower UNa excretion rates. Patients receiving higher furosemide doses were less frequently on angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers and they tended to be treated more often with mineralocorticoid receptor antagonists (**TABLE 2**). Patients with lower UNa excretion rates were older, more often male, with ischemic HF, and a higher NYHA class. Patients with low UNa excretion rates also had lower hemoglobin levels, worse renal function, and higher BNP levels. Serum sodium levels were lower and furosemide doses higher in the patients with low UNa excretion rates (**TABLE 3**). Finally, patients on higher furosemide doses and those with lower urinary sodium excretion rates had higher 5-year mortality. The association of different variables with 5-year all-cause mortality in a univariable approach is shown in Supplementary material, *Table S1*. The total 24-h UNa excretion and UNa concentration on a morning spot urine sample of the stable chronic HF patients showed a strong positive Pearson correlation coefficient ($r = 0.61$).

The receiver operating characteristic curve reflecting the ability of the ratio of furosemide dosage to UNa excretion to predict 5-year mortality is shown in **FIGURE 1**. The area under the curve was 0.75 (95% CI, 0.70–0.81; $P < 0.001$). The best cutoff point based on this curve was 0.8, with a sensitivity of 77.6%, specificity of 63.8%, positive

TABLE 2 Comparison between patients receiving low (<80 mg/day) and high (≥80 mg/day) furosemide doses

Characteristic		Low furosemide dose (n = 136)	High furosemide dose (n = 147)	*P* value
Male sex		100 (73.5)	99 (67.3)	0.26
Age, y		68 (13)	70 (13)	0.1
Arterial hypertension		79 (58.1)	98 (66.7)	0.14
Diabetes mellitus		42 (30.9)	63 (42.9)	0.04
Left ventricular function	HFpEF	8 (5.9)	11 (7.5)	0.09
	HFmrEF	30 (22.1)	18 (12.2)	
	HFrEF	98 (72.1)	118 (80.3)	
Severe LVSD		65 (47.8)	99 (67.3)	0.001
Ischemic etiology of HF		55 (40.4)	68 (46.3)	0.32
NYHA ≥II		70 (51.5)	125 (85.0)	<0.001
SBP, mm Hg		123 (21)	119 (20)	0.09
Hemoglobin, g/dl		13.2 (1.9)	12.7 (1.8)	0.03
Creatinine, mg/dl		1.16 (0.34)	1.35 (0.47)	<0.001
BNP, pg/ml, median (IQR)		150.3 (91.2–306.5)	411.2 (171.0–952.4)	<0.001
Serum Na concentration, mEq/l		139.1 (2.7)	138.9 (3.3)	0.58
UNa concentration, mEq/l		94 (31)	76 (26)	<0.001
24-h UNa excretion, mEq		167 (74)	151 (73)	0.06
β-Blocker		131 (96.3)	139 (94.6)	0.48
β-Blocker dose, mg/day, median (IQR)		25.0 (12.5–50.0)	18.7 (12.5–37.5)	0.22
ACEI and/or ARB		133 (97.8)	129 (87.8)	0.001
ACEI and/or ARB dose, mg/day, median (IQR)		10.0 (5.0–20.0)	5.0 (2.5–20.0)	0.005
MRA		36 (26.5)	59 8 (39.5)	0.02
MRA dose, mg/day, median (IQR)		0.0 (0.0–12.5)	0.0 (0.0–12.5)	0.02
Thiazide diuretics		4 (2.9)	9 (6.1)	0.26
5-year mortality		39 (28.7)	95 (64.6)	<0.001

Data are presented as number (percentage) or mean (SD) unless otherwise indicated.

SI conversion factors: see TABLE 1.

Abbreviations: LVSD, left ventricular systolic dysfunction; others, see TABLE 1

predictive value of 65.8%, and negative predictive value of 76%. The Kaplan–Meier survival curves according to the ratio of furosemide dosage to UNa concentration (with a cutoff value of 0.8) are shown in FIGURE 2. Patients with a ratio greater than or equal to 0.8 had a multivariate-adjusted hazard ratio (HR) of 5-year all-cause mortality of 2.85 (95% CI, 1.78–4.58; *P* <0.001). The multivariable model is presented in Supplementary material, *Table S2*.

When the patients were cross-classified according to both diuretic dosage and UNa concentration, 91 of them (32.2%) had a UNa concentration of 80 mEq/l or more with a furosemide dose of less than 80 mg/day, 80 (28.3%) had a UNa concentration of less than 80 mEq/l with 80 mg or more of furosemide per day, and the remaining 39.5% had an elevated UNa excretion with a high furosemide dosage or low UNa excretion with a low furosemide dosage. During follow-up, 134 patients died (47.3%). Patients with better survival were those with a UNa concentration of 80 mEq/l or more and a furosemide dose of less than 80 mg/day. Worse prognosis was associated with a UNa concentration of less than 80 mEq/l and 80 mg or more of furosemide per day. The remaining patients had an intermediate prognosis (FIGURE 3). Considering patients with a UNa concentration of 80 mEq/l or more and a furosemide dose of less than 80 mg/day as the reference category, those with a UNa concentration of less than 80 mEq/l and 80 mg or more of furosemide per day had an HR of 5-year mortality of 4.15 (95% CI, 2.31–7.45; *P* <0.001); the remaining patients had a nonsignificant 47% increase in mortality with a multivariate-adjusted HR of 1.47 (95% CI, 0.84–2.58; *P* = 0.18) (Supplementary material, *Table S3*). Importantly, the results would have been similar if the total 24-h UNa excretion or total urinary volume were considered in the multivariable model (data not shown).

DISCUSSION

The ratio of furosemide dosage to UNa concentration can be seen as an indirect measure of diuretic resistance that correlates with prognosis in chronic HF. Patients with a furosemide dosage to UNa concentration ratio of 0.8 or higher have a more than 3-fold higher probability of mortality in the next 5 years. Patients who require a furosemide dose of at least 80% of

TABLE 3 Comparison between patients with low (<80 mEq/l) and high (≥80 mEq/l) urinary sodium excretion rates

Characteristic		High UNa excretion (n = 158)	Low UNa excretion (n = 125)	*P* value
Male sex		120 (75.9)	79 (63.2)	0.02
Age, y		61 (13)	72 (12)	0.001
Arterial hypertension		91 (57.6)	86 (68.8)	0.05
Diabetes mellitus		61 (38.6)	44 (35.2)	0.56
Left ventricular function	HFpEF	9 (5.7)	10 (8)	0.48
	HFmrEF	30 (19)	18 (14.4)	
	HFrEF	119 (75.3)	97 (77.6)	
Severe LVSD		93 (58.9)	71 (56.8)	0.73
Ischemic etiology of HF		57 (36.1)	66 (52.8)	0.005
NYHA class ≥ II		97 (61.4)	98 (78.4)	0.002
SBP, mm Hg		123 (21)	119 (20)	0.17
Hemoglobin, g/dl		13.4 (1.8)	12.5 (1.9)	<0.001
Creatinine, mg/dl		1.18 (0.37)	1.36 (0.47)	0.001
BNP, pg/ml, median (IQR)		173.9 (93.9–485.1)	303.8 (155.1–788.2)	<0.001
Serum Na concentration, mEq/l		139.4 (2.6)	138.6 (3.4)	0.04
UNa concentration, mEq/l		106 (20)	59 (16)	<0.001
24-h UNa excretion, mEq		193 (69)	115 (54)	<0.001
β-Blocker		151 (95.6)	119 (95.2)	0.88
β-Blocker dose, mg/day, median (IQR)		25.0 (12.5–50.0)	12.5 (12.5–37.5)	0.09
ACEI and/or ARB		148 (93.7)	114 (91.2)	0.43
ACEI and/or ARB dose, mg/day, median (IQR)		10.0 (5.0–20.0)	5.0 (2.5–20.0)	0.007
MRA		53 (33.5)	41 (32.8)	0.89
MRA dose, mg/day, median (IQR)		0.0 (0.0–12.5)	0.0 (0.0–12.5)	0.50
Furosemide		136 (86.1)	121 (96.8)	0.002
Furosemide dose, mg, median (IQR)		60 (40–80)	80 (60–120)	<0.001
Thiazide diuretics		6 (3.8)	7 (5.6)	0.47
5-year mortality		51 (32.3)	83 (66.4)	<0.001

Data are presented as number (percentage) or mean (SD) unless otherwise indicated.

SI conversion factors: see **TABLE 1**.

Abbreviations: see **TABLES 1** and **2**

their ultimate UNa excretion rate have a diuretic resistance that is associated with a strong likelihood of serious outcomes. Patients with a ratio of less than 0.8 have a 5-year survival probability of 76%, while those with a ratio above this threshold have a 65.8% probability of mortality in the next 5 years. When each of the variables in the ratio was categorized, we observed that patients with an elevated UNa excretion rate (≥80 mEq/l) despite low furosemide doses (<80 mg/day) have the best survival, meaning that patients with less diuretic resistance have a clear survival advantage. On the other hand, patients in the upper end of diuretic inefficiency / resistance with a low UNa excretion rate (<80 mEq/l) despite an elevated furosemide dose (≥80 mg/day) have an almost 5-fold higher risk of mortality in the next 5 years compared with the former group. Our results suggest that the inability of chronic HF patients to excrete sodium in response to loop diuretics is a major prognostic determinant that underlines the significance of sodium retention in chronic HF. Patients "halfway" towards diuretic resistance—those with an elevated UNa excretion rate receiving high furosemide doses and those with low urinary excretion rates but also on low furosemide doses—represent a group with an intermediate prognosis: they have a survival advantage over the more diuretic-resistant patients, but there is a nonsignificant 69% higher risk of mortality during the next 5 years compared with the less diuretic-resistant patients.

The concept of diuretic resistance in HF reflects the inability of diuretics to control salt and water retention, even when used in appropriate and increasing dosages.[16,18] The scope of the problem is relevant, with some authors reporting a prevalence as high as 30% among HF patients, mostly among those with moderate to severe chronic HF, although the lack of a formal definition makes a true assessment extremely difficult.[2,18-20]

Predictors of diuretic resistance have already been described; diabetes, worse renal function, a higher NYHA class, and ischemic HF are among

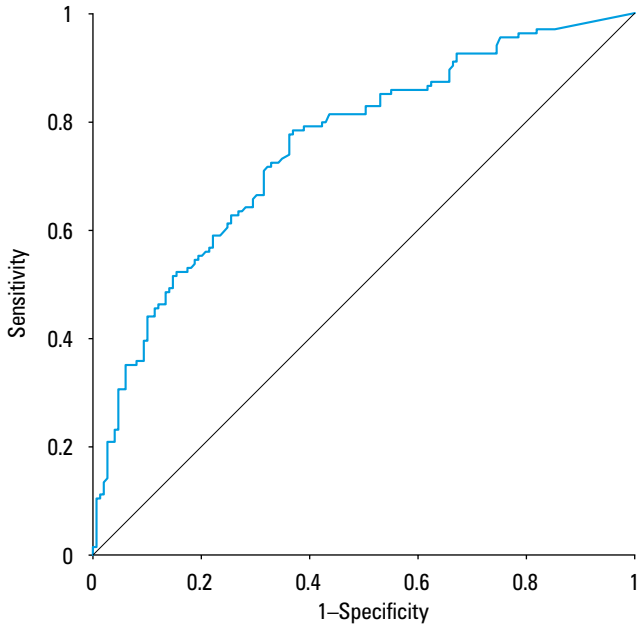

FIGURE 1 Receiver operating characteristic curve showing the association between the ratio of furosemide dosage to urinary sodium excretion and mortality in chronic heart failure. Best cutoff, 0.8; sensitivity, 77.6%; specificity, 63.8%; positive predictive value, 65.8%; negative predictive value, 76%.

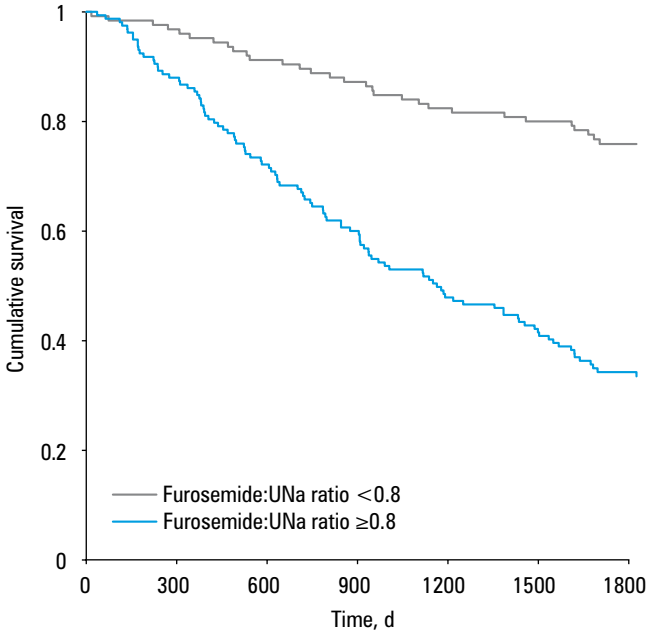

FIGURE 2 Kaplan–Meier survival curves of 5-year survival according to the ratio of furosemide dosage to urinary sodium (UNa) concentration. Patients with a ratio of 0.8 or higher have a clear survival disadvantage.

the most often recognized;[3,16,21] importantly, our results are in accordance with the existing literature regarding the profile of the diuretic-resistant patient. It should be pointed out that although glomerular filtration rate (GFR) is a known predictor of mortality and is unquestionably associated with diuretic resistance in HF, GFR alone simply reflects the filtration function of the kidneys, overlooking major components of fluid homeostasis, such as sodium avidity.[2,14] This reinforces the relevance of UNa excretion in relation to diuretic dosage in portraying diuretic resistance beyond GFR. Also, our results support previous data reporting UNa as having different biological meanings in chronic stable HF versus acute HF due to differences in volume status, diuretic dosage, and neurohormonal activation; they also highlight the need to interpret the level of this marker within the full clinical context.[22]

A myriad of mechanisms combine to create a state of diuretic resistance in chronic HF. Importantly, the activation of the renin-angiotensin-aldosterone system and the sympathetic nervous system, which closely accompany HF progression, cause increased sodium retention and reduced renal perfusion, leading to the need for progressively higher daily doses of diuretics, which ultimately perpetuates the neurohormonal activation cycle.[8] Furthermore, the nephron remodeling and compensatory mechanisms of increased distal sodium reabsorption due to chronic loop diuretic administration—the so-called *braking phenomenon*—as well as the altered diuretic pharmacokinetics all contribute to a decreased diuretic efficacy in HF patients.[9,14,16,18,22] While it is still unclear whether diuretic resistance is merely a consequence of the mechanisms that drive HF progression or it has a direct causal role in that process, it has been, nevertheless, well established that it is associated with a dire prognosis in chronic HF.[8,23] Regarding the diuretic dosage, there has been extensive debate about whether a higher diuretic dose is independently associated with mortality,[24,25] a marker of disease severity,[25,26] or both.[6] Our findings that evaluation of the diuretic dosage coupled with the UNa excretion rate can better stratify chronic HF patients in terms of mortality risk are in agreement with the hypothesis that metrics of diuretic responsiveness overcome the questions raised above, yielding more prognostic information than the diuretic dosage alone and translating into a measure of diuretic resistance.[3,16]

The study has important limitations that ought to be mentioned. It is a single-center study of a very particular group of chronic HF patients, followed in an HF clinic of a tertiary care academic hospital; therefore, the results may be difficult to generalize. The small sample size is a concern as well. However, the long follow-up period is a strength of our study and, in fact, the number of events analyzed was enough to detect an independent association between the furosemide dosage to UNa concentration ratio and mortality as well as the existence of groups of patients with different degrees of diuretic resistance with clearly different clinical trajectories. The fact that the population was heterogeneous, including patients with HFpEF, HFmrEF, and HFrEF, is also a concern. A stratified analysis of groups according to ejection fraction was not possible due to the sample size, so the study should eventually be repeated for each HF subgroup, since kidney involvement is likely different between them.[27-29] The patients of this study

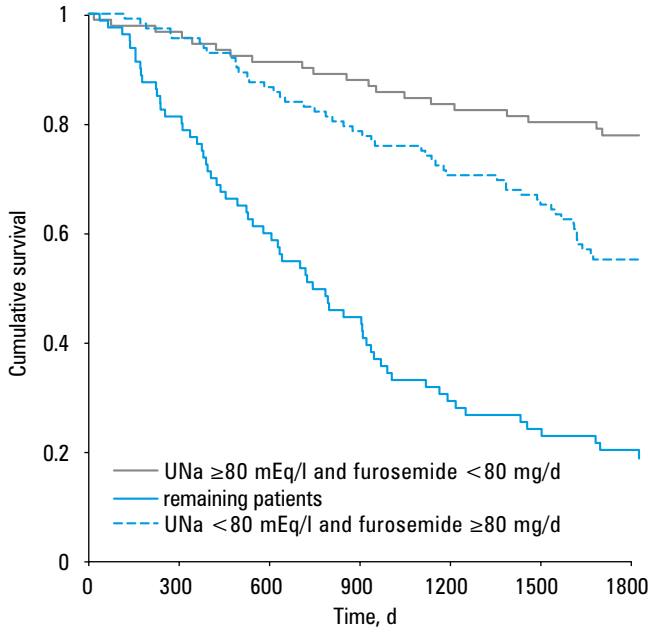

FIGURE 3 Kaplan–Meier curves of 5-year survival according to the cross-classification considering urinary sodium (UNa) excretion and daily furosemide dose

were recruited before the approval of angiotensin receptor-neprilysin inhibitors in HF treatment and, therefore, despite being a twenty-first–century cohort, it is not a completely contemporary population of HF patients. The use of sodium-glucose cotransporter 2 inhibitors was also not considered and liberalized at the time of recruitment, though such drugs would expectably alter the urinary output and, consequently, the UNa concentration. The results need to be reproduced in a contemporary HF cohort.

Notwithstanding the abovementioned limitations, this is, to our best knowledge, the first study to address the impact of UNa excretion in chronic HF. We report that the combination of the daily furosemide dosage and UNa concentration can stratify stable HF patients in terms of long-term mortality risk. Patients with elevated UNa excretion rates who are receiving low furosemide dosages have better prognosis, while those with low sodium excretion rates despite high furosemide doses present a clear survival disadvantage. Patients with a furosemide dosage to UNa concentration ratio greater than or equal to 0.8 have a more than 3-fold higher probability of mortality in the next 5 years, while 76% of those with lower ratios will be alive 5 years later. We additionally propose the furosemide dosage to UNa excretion ratio as an indirect measure of diuretic resistance.

Conclusions The daily diuretic dosage and UNa excretion should be evaluated together to refine risk stratification in patients with chronic HF. An equally interesting application of these measurements would be their potential to help determine the optimal diuretic dosage for each patient, beyond the clinical signs of volume status and change in GFR.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

CONTRIBUTION STATEMENT JPA, PB, and PL came up with the conceptualization and methodology of the article. PL analyzed the obtained data. DO, MS-C, and MA were responsible for data collection. CE prepared the original draft of the paper. All authors contributed to reviewing and editing of the written manuscript and approve of its final version.

CONFLICT OF INTEREST None declared.

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