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Differential mortality association of loop diuretic dosage according to blood urea nitrogen and carbohydrate antigen 125 following a hospitalization for acute heart failure

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Aims Recent observations in chronic stable heart failure suggest that high-dose loop diuretics (HDLDs) have detrimental prognostic effects in patients with high blood urea nitrogen (BUN), but recent findings have also indicated that diuretics may improve renal function. Carbohydrate antigen 125 (CA125) has been shown to be a surrogate of systemic congestion. We sought to explore whether BUN and CA125 modulate the mortality risk associated with HDLDs following a hospitalization for acute heart failure (AHF).

Methods and results We analysed 1389 consecutive patients discharged for AHF. CA125 and BUN were measured at a mean of 72 ± 12 h after admission. HDLDs (≥120 mg/day in furosemide equivalent dose) were interacted to a four-level variable according to CA125 (>35 U/mL) and BUN (above the median), and related to all-cause mortality. At a median follow-up of 21 months, 561 (40.4%) patients died. The use of HDLDs was independently associated with increased mortality [hazard ratio (HR) 1.23, 95% confidence interval (CI) 1.01–1.50], but this association was not homogeneous across CA125–BUN categories (*P* for interaction <0.001). In patients with normal CA125, use of HDLDs was associated with high mortality if BUN was above the median (HR 2.29, 95% 1.51–3.46), but not in those with BUN below the median (HR 1.22, 95% CI 0.73–2.04). Conversely, in patients with high CA125, HDLDs showed an association with increased survival if BUN was above the median (HR 0.73, 95% CI 0.55–0.98) but was associated with increased mortality in those with BUN below the median (HR 1.94, 95% CI 1.36–2.76).

Conclusion The risk associated with HDLDs in patients after hospitalization for AHF was dependent on the levels of BUN and CA125. The information provided by these two biomarkers may be helpful in tailoring the dose of loop diuretics at discharge for AHF.

Keywords Loop diuretics • Mortality • Acute heart failure • Carbohydrate antigen 125 • Blood urea nitrogen

Introduction

Loop diuretics are nearly universally used for relieving symptoms of systemic congestion in patients with heart failure (HF), especially during episodes of clinical decompensation.[1,2] Paradoxically, a number of studies[3–6] have reported an increased risk for adverse outcomes associated with higher doses of loop diuretic treatment. Furthermore, the optimal use of loop diuretics remains a real clinical challenge, and their dose titration is largely intuitive.

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Blood urea nitrogen (BUN) is a well-known marker of renal function, and hence its serum concentrations vary according to changes in glomerular filtration rate (GFR). Recent studies[7–9] have also shown that BUN correlates with neurohormonal activation parameters. Testani *et al.*[9] reported a significant interaction between high-dose loop diuretics (HDLDs) and BUN in a selected cohort of 2456 compensated HF patients with left ventricular ejection fraction (LVEF) $\leq$ 35%. These authors found that the risk associated with HDLD use was strongly dependent on BUN concentrations, with reduced survival when BUN was above the median.

On the other hand, recent studies[10–13] have also highlighted the importance of venous congestion in the pathophysiology of renal dysfunction in HF. For instance, a recent study by Damman *et al.*[13] suggested that furosemide may prevent tubular renal injury in a small group of patients with HF. Nevertheless, it is recognized that the accuracy of symptoms and signs for quantifying systemic congestion in HF is limited.[14] In this regard, various studies[15–18] have suggested that the serum tumour marker carbohydrate antigen 125 (CA125) may be a reliable surrogate for systemic congestion, and associated with adverse outcomes in acute and chronic HF. Thus, we hypothesize that the prognostic effect of HDLDs is modulated by the balance between the beneficial decongestion vs. the negative neurohormonal effect.

We sought to explore, in a cohort of patients hospitalized with acute heart failure (AHF), the relationship between discharge HDLD and all-cause mortality, and whether the association is modulated by surrogate markers of systemic congestion (CA125) and renal dysfunction/neurohormonal activation (BUN).

Methods

Study group and protocol

We prospectively studied a cohort of 1538 patients consecutively admitted to the cardiology department from a tertiary hospital (Hospital Clínico Universitario de Valencia) with the diagnosis of AHF. AHF was defined according to current guidelines.[1,2,19] Patients were followed-up from hospital discharge occurring between 1 January 2004 and 9 March 2011. By design, patients who died ($n = 80$) or received a heart valve replacement during the index hospitalization were excluded ($n = 69$), leaving 1389 patients as the study sample. In addition, patients with a final diagnosis of acute coronary syndrome, active sepsis/pneumonia, terminal cancer, or end-stage renal disease on dialysis were excluded from the study. Demographic information, medical history, vital signs, 12-lead electrocardiogram, and laboratory and drug utilization data were routinely determined on admission and throughout the hospital course, using pre-established registry questionnaires. All patients received intravenous treatment with furosemide for at least the first 48 h. LVEF was assessed with echo (Agilent Sonos 5500-Phillips) during the index hospitalization. Treatment with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, aldosterone antagonists, anticoagulants, diuretics, and other therapeutic strategies were individualized following established guidelines operating at the time the patient was recruited in the registry.[1,2,19]

Outcomes

Patients were followed-up until death, lost to follow-up, valve replacement, or cardiac transplantation. All-cause mortality was selected as the main endpoint, and cardiovascular (CV) mortality as a secondary endpoint. The information regarding the cause of death was extracted from the patients' clinical chart, and adjudicated by an investigator who was blinded to the hypothesis of the study. Deaths related to CV aetiology included sudden death, progressive HF death, and other CV-related deaths. Moreover, those patients who died outside the hospital ($n = 157$), in which the circumstances concerning the death were unknown, were assumed to be CV in origin for the purpose of analysis. This study conforms to the principles outlined in the Declaration of Helsinki and was approved by an institutional review committee. All patients gave informed consent.

Blood urea nitrogen and carbohydrate antigen 125 measurements

Blood urea nitrogen and serum CA125 were obtained simultaneously during patients' hospitalization (at a mean of 72 $\pm$ 12 h after admission). CA125 was measured using commercially available immunoassay kits (Elecsys CA125 II assay-Roche Diagnostics) and BUN was measured using a kinetic test with urease (Roche-Hitachi systems cobas c). A derived variable was constructed dichotomizing BUN by its median ($<$ 24.8 mg/dL or $\geq$ 24.8 mg/dL) and serum CA125 by its upper limit of normality ($<$35 U/mL or $\geq$ 35 U/mL). Hence, the study sample was stratified on the following four categories: C1 ($n = 239$), with low CA125 and high BUN; C2 ($n = 269$), with low CA125 and low BUN; C3 ($n = 437$), with high CA125 and low BUN; and C4 ($n = 444$), with high CA125 and high BUN.

Loop diuretic treatment

Overall, patients' treatment decisions were left at the discretion of the cardiologist in charge of the patient. No specific recommendations regarding prescription of diuretics were followed according to the levels of any marker. All patients were discharged on diuretics (furosemide = 69.1%, torasemide = 24.9%, furosemide + hydrochlorothiazide (HCTZ) = 4.2%, torasemide + HCTZ = 1.44%, and HCTZ alone = 0.36%). Total loop diuretic dose (mg/day) was converted to furosemide equivalent dose (FED) following the equation used by Levy *et al.*[20] The conversion used was furosemide 80 mg = torasemide 40 mg = HCTZ 25 mg. HCTZ contributed only when added to loop diuretics. Thus, five patients were included in the analysis with FED = 0. For the association with mortality risk, FED was explored as continuous and dichotomized according to a pre-specified cut-off point used to define HDLD ($\geq$ 120 mg/day).

Statistical analysis

Continuous variables with and without symmetrical distributions were expressed as mean $\pm$ SD and median [interquartile range (IQR)], respectively. For their comparison, Student's *t*-test, analysis of variance (ANOVA), or Kruskal–Wallis rank test was used as appropriate. Discrete variables were presented as percentages and compared with χ^2 test. HDLD mortality rates were depicted among BUN–CA125 categories using the Kaplan–Meier method, and their differences tested by the Peto–Peto Prentice test. As a pre-specified hypothesis, we intentionally tested for homogeneity of the effect of continuous and dichotomized FED (into HDLD $\geq$120 mg/day) on mortality among the CA125–BUN categories. Multivariable analysis for all-cause mortality was performed by using a flexible parametric survival analysis described by Royston *et al.*[21] Baseline hazard function was modelled with three degrees of freedom (df) restrictive cubic splines (RCS).

Candidate covariates for the initial multivariable model were chosen based on previous medical knowledge, and regardless of their *P*-value. Then, a reduced, although highly predictive model, was derived by backward elimination using a 'multivariable fractional polynomial' algorithm.[22]The final model included as covariates age, gender, obesity, prior admission for AHF, last known New York Heart Association (NYHA) class before admission (under stable conditions), hypertension, diabetes mellitus, history of myocardial infarction, dementia, systolic blood pressure, LVEF <50%, heart rate, atrial fibrillation, serum creatinine, hyponatraemia (sodium <135 mEq/L), anaemia (haemoglobin ≤ 12 g/L for women and ≤ 13 g/L for men), brain natriuretic peptide, high sensitivity C-reactive protein, and treatment with beta-blockers, oral anticoagulants, statins, and mineralcorticoid receptor inhibitors. For CV mortality, a multivariable competing risks analysis[23] was used, and the estimates are presented as the subdistribution hazard rate (SHR) with 95% confidence intervals (CIs). The CV mortality final model included a similar set of covariates to that of the main model. The proportionality assumption for the hazard function over time was tested by interacting the variables retained in the final model with time. Anaemia, use of angiotensin-converting enzyme inhibitors, and hypertension were included in the final models with time-dependent effects. HDLD mortality rates [expressed as per 10 person-years (PYs)] were estimated from the multivariable regression model. The performance of the survival models was assessed by the Harrell's C-statistic. A two-sided *P*-value of <0.05 was considered to be statistically significant for all analyses. All analyses were performed using Stata 12 (StataCorp, 2011, Stata Statistical Software: Release 12. College Station, TX, USA).

Results

The mean age in our sample was 72.7 ± 11.5 years; 51% were female, 46.6% exhibited LVEF >50%, 37.9% had prior history of ischaemic heart disease, and median length of stay was 7 days (5–11). The medians (IQR) for FED, BUN, and serum CA125 were 80 (40–100) mg/day, 24.8 (19.2–33.6) mg/dL, and 54 (24–125) U/mL, respectively. All-cause mortality rates are depicted through Kaplan–Meier curves in Supplementary material, *Figure S1*. Overall, CA125 and BUN markers identified four subpopulations that differ in most of the indicators of disease severity (*Table 1*). Indeed, patients in C1 and C4 showed the worst baseline risk profile, including higher dose of HDLDs (24% and 33%, respectively, as compared with 17% and 21% for C2 and C3) and the higher mortality risk (Supplementary material, *Figure S1*). Moreover, patients receiving HDLDs (24.4% of our population) were shown to be sicker and exhibited higher mortality rates (*Table 2*). The adjusted interaction between CA125 (>35 U/mL/ ≤ 35 U/mL) and BUN (above/below the median) was not significant ($P = 0.930$), indicating that the prognostic value of high CA125 did not differ substantially according to BUN status.

Loop diuretics and mortality

At a median follow-up of 1.72 years (IQR = 0.61–3.55), 561 (40.4%) patients died. Of these 561 deaths, 404 (72%) were documented as being CV-related deaths. As regards the entire population, HDLD was independently associated with all-cause mortality (HR 1.23, 95% CI 1.01–1.50; $P = 0.04$). As a main effect, continuous FED (transformed as FEDsqrt) was positively associated with mortality, although such an association did not achieve statistical significance (HR 1.03, 95% CI 0.99–1.06, $P = 0.16$).

Furosemide equivalent dose and all-cause mortality across carbohydrate antigen 125–blood urea nitrogen categories

Continuous FED was tested against mortality with a df(4) RCS, and interacting with CA125–BUN categories (*P* for interaction = 0.0034). The *P*-value for linearity supports the lack of linearity in the risk function for FED ($P = 0.001$). *Figure 1* shows a differential adjusted risk between the continuum of FED and mortality across CA125–BUN categories, in terms of HR, with the value of FED 40 mg/day used as reference. As FED increased above 40 mg/day, the HR for mortality increased in C1 (low CA125/high BUN) and C3 (high CA125/low BUN) categories (*Figure 1A* and *C*, respectively). In C2 (low CA125/low BUN), increases in FED translated into a neutral effect on mortality (*Figure 1B*). However, increases in FED for patients in C4 (high CA125/high BUN) were associated with marginal survival benefit (*Figure 1D*).

The analysis dichotomizing FED into HDLD (≥ 120 mg/day) also revealed a significant interaction with CA125–BUN categories (*P* for interaction <0.001). The corresponding adjusted estimates are presented in *Table 3*. HDLDs were associated with an increased risk of mortality in patients with low CA125 and BUN above the median (C1), but not in those below the median (C2). Conversely, in patients with high CA125, the administration of HDLDs showed a survival benefit only if BUN was above the median (C4); for those with BUN below the median, it became a significant risk factor for mortality.

In order to understand the disease course and the potential basis for the above HRs, we estimated the baseline hazard function among those patients with and without HDLD and plotted against follow-up time. *Figure 2* shows the adjusted mortality rates (expressed as per 10 PYs) at each BUN–CA125 category. The highest death rates correspond to patients on HDLDs which belong to groups C1 and C3 (10 deaths per 10 PYs, approximately) (*Figure 2A* and *C*). For patients in C2, death rates among those on HDLDs were similar (*Figure 2B*). For C4 (*Figure 2D*), death rates were higher for those on HDLDs = 0 (8.5 deaths per 10 PYs, approximately) compared with those taking HDLDs (6 deaths per 10 PYs). These figures are also telling us that overall, the death rate seems to be highest ~ 1 year after discharge, and it decreases after that time to plateau at ~4 years.

Furosemide equivalent dose and cardiovascular mortality across carbohydrate antigen 125–blood urea nitrogen categories

High-dose loop diuretics also proved to be independently associated with CV mortality, with an effect that varied according to BUN–CA125 categories. The direction and strength of the association are similar to those of all-cause mortality (*Table 3*).

Table 1 Baseline characteristics of the population stratified by carbohydrate antigen 125 and blood urea nitrogen status

Variables	C1 (n = 239)	C2 (n = 269)	C3 (n = 437)	C4 (n = 444)	Omnibus P-value
Demographic and medical history					
Age, years	76 ± 9	70 ± 12	69 ± 13	76 ± 9	<0.001
Male, *n* (%)	109 (45.6)	117 (43.5)	229 (52.4)	225 (50.7)	0.076
Previous admission for AHF, *n* (%)	142 (59.4)	181 (67.3)	321 (73.5)	267 (60.1)	<0.001
LOS, days[a]	7 (5–10)	7 (5–9)	7 (5–11)	8 (6–12.5)	0.001
Hypertension, *n* (%)	215 (90)	214 (79.6)	302 (69.1)	358 (80.6)	<0.001
Diabetes mellitus, *n* (%)	98 (41.0)	105 (39.0)	165 (37.8)	211 (47.5)	0.020
Dyslipidaemia, *n* (%)	119 (49.8)	130 (48.3)	162 (37.1)	221 (49.8)	<0.001
Current smoker, *n* (%)	12 (5.0)	40 (14.9)	62 (14.2)	50 (11.3)	0.001
Previous smoker, *n* (%)	51 (21.3)	47 (17.5)	95 (21.7)	93 (20.9)	0.558
Ischaemic heart disease, *n* (%)	100 (41.8)	91 (33.8)	145 (33.2)	191 (43)	0.006
Valvular heart disease, *n* (%)	52 (21.8)	60 (22.3)	109 (24.9)	114 (25.7)	0.580
ADHF, *n* (%)	142 (59.4)	156 (58)	336 (76.9)	327 (73.6)	<0.001
Acute pulmonary oedema, *n* (%)	61 (25.5)	78 (29.0)	68 (15.6)	84 (18.9)	<0.001
Hypertensive AHF, *n* (%)	32 (13.4)	34 (12.6)	31 (7.1)	22 (5.0)	<0.001
NYHA class III/IV, *n* (%)[b]	51 (21.3)	33 (12.3)	67 (15.3)	102 (23.0)	0.001
Previous HF, *n* (%)	81 (33.9)	82 (30.5)	106 (24.3)	155 (34.9)	0.004
Previous MI, *n* (%)	70 (29.3)	62 (23)	98 (22.4)	142 (32.0)	0.005
COPD, *n* (%)	56 (23.4)	54 (20.1)	83 (19)	103 (23.2)	0.358
PAD, *n* (%)	30 (12.6)	16 (5.9)	28 (6.4)	37 (8.3)	0.020
Stroke, *n* (%)	25 (10.5)	18 (6.7)	39 (8.9)	56 (12.6)	0.063
Renal failure, *n* (%)	72 (30.1)	11 (4.1)	18 (4.1)	126 (28.4)	<0.001
Radiological pleural effusion, *n* (%)	57 (23.8)	64 (23.8)	243 (55.6)	253 (57)	<0.001
Peripheral oedema, *n* (%)	105 (43.9)	123 (45.7)	270 (61.8)	297 (66.9)	<0.001
Previous use of diuretics, *n* (%)	150 (62.8)	149 (55.4)	209 (47.8)	321 (72.3)	<0.001
Previous use of beta-blockers, *n* (%)	63 (26.4)	67 (24.9)	98 (22.4)	125 (28.2)	0.265
Previous use of ACEIs, *n* (%)	126 (52.7)	130 (48.3)	153 (35)	211 (47.5)	<0.001
Previous use of ARBs, *n* (%)	10 (4.2)	10 (3.7)	17 (3.9)	11 (2.5)	0.582
Previous use of statins, *n* (%)	84 (35.1)	92 (34.2)	115 (26.3)	151 (34)	0.029
Vital signs					
Heart rate, b.p.m.	98 ± 28	105 ± 31	105 ± 29	99 ± 30	0.001
SBP, mmHg	155 ± 39	159 ± 38	150 ± 34	145 ± 34	<0.001
DBP, mmHg	83 ± 21	87 ± 22	85 ± 19	79 ± 19	<0.001
Electrocardiogram					
Atrial fibrillation, *n* (%)	85 (35.6)	106 (39.4)	203 (46.5)	209 (47.1)	0.008
QRS >120 ms, *n* (%)	77 (32.2)	87 (32.3)	113 (25.9)	145 (32.7)	0.103
Laboratory					
Haemoglobin, g/dL	12.5 ± 1.8	13.2 ± 1.9	12.7 ± 1.8	12.2 ± 1.9	<0.001

Continued

Table I *Continued*

Variables	C1 (n = 239)	C2 (n = 269)	C3 (n = 437)	C4 (n = 444)	Omnibus P-value
Serum creatinine, mg/dL	1.55 ± 0.73	1.02 ± 0.26	1.02 ± 0.31	1.55 ± 0.65	<0.001
BUN, mg/dL	38.5 ± 15	19.2 ± 3.6	18.8 ± 3.9	37.7 ± 13.1	<0.001
Uric acid, mg/dL	8.5 ± 2.3	7.0 ± 2	7.2 ± 2	8.7 ± 2.5	<0.001
Sodium, meq/L	139.3 ± 3.6	139.4 ± 4.7	138.7 ± 4.6	138.9 ± 4.8	0.145
Troponin I, ng/mL[a]	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0.001
Troponin I >0.2 ng/mL, *n* (%)	68 (28.5)	60 (22.3)	67 (15.3)	107 (24.1)	<0.001
BNP, pg/mL[a]	128 (70–226)	110 (72–176)	156 (94–270)	208 (101–378)	<0.001
Relative lymphocyte count, %	19 ± 11	20 ± 11	18 ± 10	17 ± 11	0.008
CA125, U/mL[a]	19 (13–27)	19 (14–25)	102 (62–183)	97 (56–169)	<0.001
Total cholesterol, mg/dL	176.3 ± 43.2	182.8 ± 42.3	167 ± 44.5	160.4 ± 43.3	<0.001
Triglycerides, mg/dL	137.1 ± 71.7	127 ± 59.2	107.8 ± 50.3	118.3 ± 53	<0.001
Echocardiography					
LVEF, %	53.2 ± 14.3	52.2 ± 15.5	48.4 ± 15.8	49.3 ± 15.5	<0.001
LVEF ≤50%, *n* (%)	88 (36.8)	109 (40.5)	220 (50.3)	230 (51.8)	<0.001
LAD, mm	41.3 ± 7.6	42.2 ± 7.2	44.2 ± 8	43.8 ± 7.7	<0.001
LVDD, mm	54.9 ± 9	55.2 ± 9.9	56.2 ± 9.9	55.8 ± 9.7	0.307
Medical treatment					
Beta-blockers, *n* (%)	136 (56.9)	152 (56.5)	270 (61.8)	238 (53.6)	0.104
Diuretics, *n* (%)	239 (100)	269 (100)	437 (100)	444 (100)	1.00
HDLDs, *n* (%)	58 (24.3)	45 (16.7)	90 (20.6)	146 (32.9)	<0.001
Furosemide equivalent dose, mg/day[a]	80 (40–80)	80 (40–80)	80 (40–80)	80 (40–120)	<0.001
Mineralcorticoid receptor inhibitors, *n* (%)	39 (16.3)	56 (20.8)	144 (33)	83 (18.7)	<0.001
ACEIs, *n* (%)	86 (36)	119 (44.2)	190 (43.5)	152 (34.2)	0.008
ARBs, *n* (%)	76 (31.8)	92 (34.2)	123 (28.1)	143 (32.2)	0.351
Oral anticoagulants, *n* (%)	86 (36)	106 (39.4)	188 (43)	183 (41.2)	0.334
Nitrates, *n* (%)	56 (23.4)	40 (14.9)	60 (13.7)	107 (24.1)	<0.001
Digoxin, *n* (%)	46 (19.2)	64 (23.8)	129 (29.5)	105 (23.6)	0.022
Outcomes					
All-cause mortality, *n* (%)	102 (42.7)	79 (29.4)	141 (32.3)	239 (53.8)	<0.001
Cardiovascular mortality, *n* (%)	75 (31.4)	50 (18.6)	97 (22.2)	182 (41.0)	<0.001
Follow-up time, years[a]	1.5 (0.7–3.4)	2.1 (0.9–4.2)	2.0 (0.6–3.9)	1.4 (0.5–3.0)	<0.001

Values are expressed as mean ± SD, unless otherwise specified; categorical variables are presented as percentages.
CA125 and BUN categories: C1, CA125 ≤35 U/mlL and BUN above the median; C2, CA125 ≤35 U/mL and BUN below the median; C3, CA125 >35 U/mL and BUN below the median; C4, CA125 >35 U/mL and BUN above the median.
ACEI, angiotensin-converting enzyme inhibitor; ADHF, acute decompensated heart failure; AHF, acute heart failure; ARB, angiotensin II receptor blocker; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CA125, carbohydrate antigen 125; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; HDLD, high-dose loop diuretic; HF, heart failure; LAD, left atrial diameter; LOS, length of stay; LVDD, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PAD, peripheral artery disease; SBP, systolic blood pressure.
[a]Value presented as the median (interquartile range).
[b]Last NYHA functional class measured under clinically stable conditions.

Table 2 Baseline characteristics of the population according to furosemide equivalent dose at discharge

Variables	Furosemide equivalent dose <120 mg/day (*n* = 1050)	Furosemide equivalent dose ≥120 mg/day (*n* = 339)	*P*-value
Demographic and medical history			
Age, years	72 ± 12	74 ± 11	0.029
Male, *n* (%)	510 (48.6)	170 (50.1)	0.618
Previous admission for AHF, *n* (%)	746 (71)	165 (48.7)	<0.001
Hypertension, *n* (%)	812 (77.3)	277 (81.7)	0.095
Diabetes mellitus, *n* (%)	408 (38.9)	171 (50.4)	<0.001
Dyslipidaemia, *n* (%)	469 (44.7)	163 (48.1)	0.286
Current smoker, *n* (%)	129 (12.3)	35 (10.3)	0.384
Previous smoker, *n* (%)	216 (20.6)	70 (20.6)	1.000
Ischaemic heart disease, *n* (%)	378 (36)	149 (44)	0.010
Valvular heart disease, *n* (%)	238 (22.7)	97 (28.6)	0.029
ADHF, *n* (%)	714 (68)	247 (72.9)	0.104
Acute pulmonary oedema, *n* (%)	225 (21.4)	66 (19.5)	0.490
Hypertensive AHF, *n* (%)	98 (9.3)	21 (6.2)	0.075
Previous HF, *n* (%)	265 (25.2)	159 (46.9)	<0.001
Previous MI, *n* (%)	256 (24.4)	116 (34.2)	0.001
COPD, *n* (%)	222 (21.1)	74 (21.8)	0.819
PAD, *n* (%)	76 (7.2)	35 (10.3)	0.083
Stroke, *n* (%)	105 (10)	33 (9.7)	1.000
Renal failure, *n* (%)	145 (13.8)	82 (24.2)	<0.001
Radiological pleural effusion, *n* (%)	423 (40.3)	194 (57.2)	<0.001
Peripheral oedema, *n* (%)	568 (54.1)	227 (67)	<0.001
Previous use of diuretics, *n* (%)	559 (53.2)	270 (79.6)	<0.001
Previous use of beta-blockers, *n* (%)	270 (25.7)	83 (24.5)	0.668
Previous use of ACEI, *n* (%)	451 (43)	169 (49.9)	0.028
Previous use of ARB, *n* (%)	37 (3.5)	11 (3.2)	1.000
Previous use of statins, *n* (%)	334 (31.8)	108 (31.9)	1.000
Vital signs			
Heart rate, b.p.m.	104 ± 31	97 ± 25	<0.001
SBP, mmHg	153 ± 36	145 ± 36	0.001
DBP, mmHg	85 ± 21	78 ± 18	<0.001
Electrocardiogram			
Atrial fibrillation, *n* (%)	452 (43)	151 (44.5)	0.659
QRS >120 ms, *n* (%)	311 (29.6)	111 (32.7)	0.278
Laboratory			
Haemoglobin, g/dL	12.7 ± 1.9	12.4 ± 1.8	0.005
Serum creatinine, mg/dL	1.23 ± 0.53	1.45 ± 0.68	<0.001
BUN, mg/dL	27.1 ± 12.8	32 ± 16.1	<0.001
Uric acid, mg/dL	7.7 ± 2.3	8.3 ± 2.6	<0.001
Sodium, meq/L	139.1 ± 4.5	138.7 ± 4.8	0.133
Troponin I, ng/mL[a]	0 (0–0.1)	0 (0–0.06)	0.083
Troponin I >0.2 ng/mL, *n* (%)	230 (21.9)	72 (21.2)	0.821
BNP, pg/mL[a]	140 (84–252)	195 (98–356)	<0.001
Relative lymphocyte count, %	19 ± 11	17 ± 9	0.001
CA125, U/mL[a]	51 (24–113)	70 (29–165)	<0.001
Total cholesterol, mg/dL	172.2 ± 44	161.5 ± 44	<0.001
Triglycerides, mg/dL	121.6 ± 58.4	114.6 ± 56.3	0.051
Echocardiography			
LVEF, %	50.9 ± 15.3	48.3 ± 15.9	0.008
LVEF ≤50%, *n* (%)	465 (44.3)	182 (53.7)	0.003

Continued

Table 2 *Continued*

Variables	Furosemide equivalent dose <120 mg/day (*n* = 1050)	Furosemide equivalent dose ≥120 mg/day (*n* = 339)	*P*-value
LAD, mm	42.5 ± 7.2	45.1 ± 9	<0.001
LVDD, mm	55.1 ± 9.5	57.5 ± 10.1	<0.001
Medical treatment			
Beta-blockers, *n* (%)	621 (59.1)	175 (51.6)	0.016
Diuretics, *n* (%)	1050 (100.0)	339 (100.0)	1.00
Furosemide equivalent dose, mg/day[a]	60 (40–80)	120 (120–120)	<0.001
Mineralcorticoid receptor inhibitors, *n* (%)	223 (21.2)	99 (29.2)	0.003
ACEI, *n* (%)	426 (40.6)	121 (35.7)	0.125
ARB, *n* (%)	334 (31.8)	100 (29.5)	0.459
Oral anticoagulants, *n* (%)	430 (41)	133 (39.2)	0.611
Nitrates, *n* (%)	179 (17)	84 (24.8)	0.002
Digoxin, *n* (%)	254 (24.2)	90 (26.5)	0.386
Outcomes			
All-cause mortality, *n* (%)	352 (33.5)	209 (61.7)	<0.001
Cardiovascular mortality, *n* (%)	259 (24.7)	145 (42.8)	<0.001
Follow-up time, years[a]	1.8 (0.7–3.6)	1.5 (0.5–3.5)	0.048

Values are expressed as mean ± standard deviation, unless otherwise specified; categorical variables are presented as percentages.
ACEI, angiotensin-converting enzyme inhibitor; ADHF, acute decompensated heart failure; AHF, acute heart failure; ARB, angiotensin II receptor blocker; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CA125, carbohydrate antigen 125; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; HF, heart failure; LAD, left atrial diameter; LVDD, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PAD, peripheral artery disease; SBP, systolic blood pressure.
[a]Value presented as the median (interquartile range).

Furosemide equivalent dose and all-cause mortality across serum carbohydrate antigen 125–estimated glomerular filtration rate categories

In a sensitivity analysis, a composite variable (CA125–eGFR) with four categories was created, with eGFR dichotomized at 45 mL/min/m^2, and CA125 at 35 U/mL. The multivariable model for all-cause mortality that included CA125–eGFR had the same set of covariates as the CA125–BUN model. The *P*-value for the interaction was significant ($P = 0.001$). This sensitivity analysis confirmed the presence of a differential effect of HDLD on mortality, with estimates pointing to the same direction as in the CA125–BUN model (*Table 3*). It is worth mentioning that the effect of HDLDs in C4 was not significant ($P = 0.135$); moreover, the discriminative accuracy of using eGFR instead of BUN decreased (Harrell's C-statistics = 0.741 vs. 0.770) (*Table 3*).

Discussion

The principal finding of this hypothesis-generating study is that the mortality risk associated with the prescription of HDLDs at discharge is differentially dependent on CA125 and BUN serum values. Loop diuretics are viewed as a double-edged sword; on the one hand, they are very effective in relieving symptoms of systemic and pulmonary congestion in patients with AHF; on the other hand, their use, particularly in high doses, has been associated with increased mortality.[3–6] In the absence of well-designed randomized studies, it has been very difficult to determine if the associated increased risk in mortality merely represents a spurious association due to confounding by indication, as has been suggested by recent findings.[24,25] or a real effect. In reference to this topic, direct roles, by promoting renal dysfunction and stimulating multiple neurohormonal systems [including the renin–angiotensin–aldosterone system (RAAS) activity], have been proposed as crucial factors explaining the diuretic-associated detrimental effects.[25–28] A recent study showed in a selected cohort of 2456 compensated HF patients with LVEF ≤ 35% that high BUN (>21 mg/dL) identified those with an increased risk of mortality when HDLDs (≥ 160 mg/day) were prescribed.[9] Given that urea tubular reabsorption is largely dependent on neurohormonal activation,[29,30] these authors proposed that an elevated BUN level, in addition to being a marker related to reduction of glomerular filtration, may act as surrogate for RAAS activity.[7–9,30]

In other respects, it is also known that diuretics sometimes improve renal function,[26,27] and recent studies have highlighted the role of venous congestion rather than reduced arterial renal perfusion in the pathophysiology of renal function impairment observed in HF.[10–13] For instance, recent works have shown that elevated intra-abdominal and central venous pressure, but

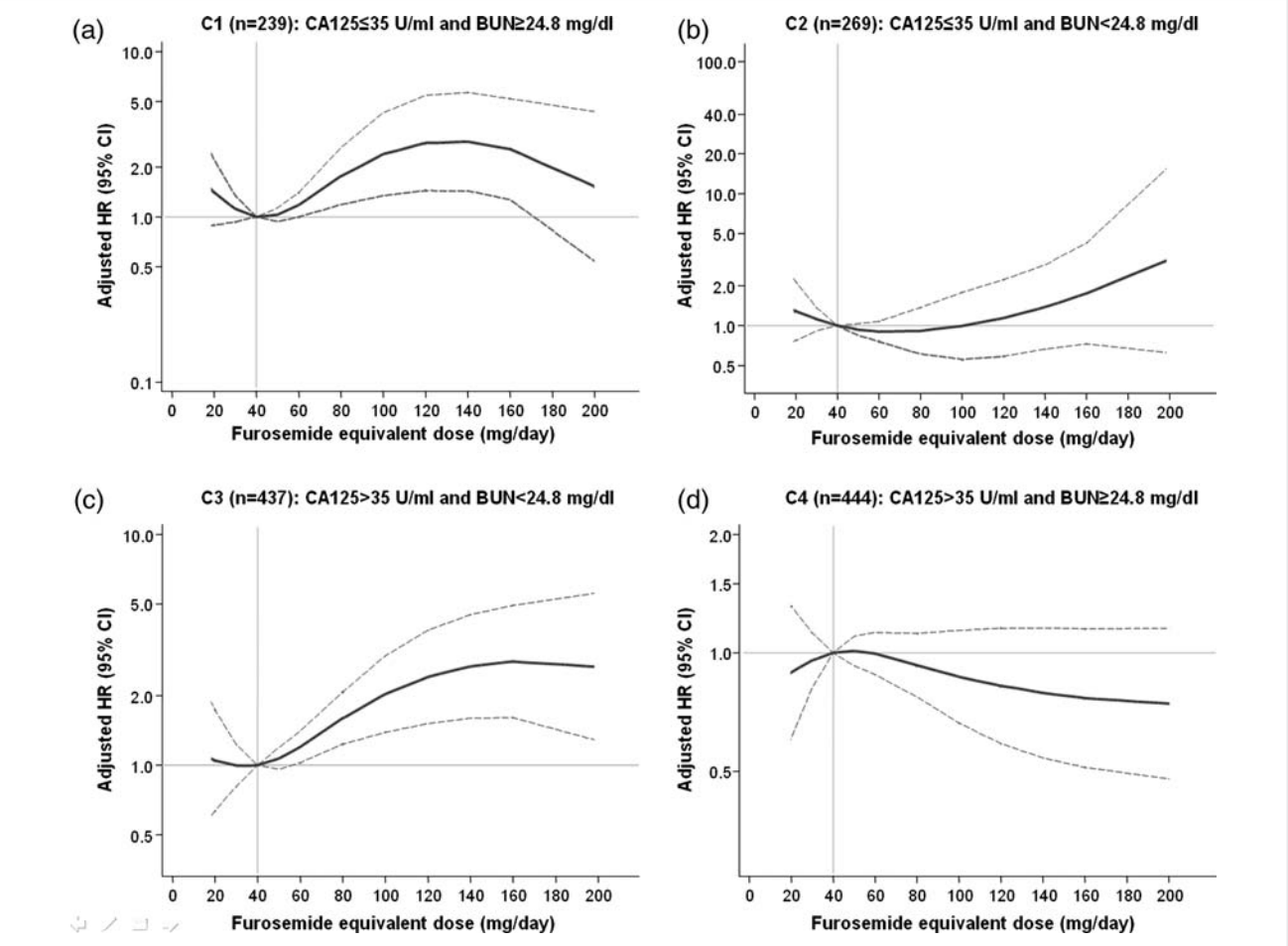

Figure 1 Adjusted hazard ratios (and their 95% pointwise confidence intervals) for the effect of FED on mortality at each BUN–CA125 category. FED is modelled with df(4) RCS. Hazard ratios are calculated against the value of 40 mg/day as reference point. BUN, blood urea nitrogen; CA125, carbohydrate antigen 125; CI, confidence interval; FED, furosemide equivalent dose; HR, hazard ratio; RCS, restricted cubic splines.

not cardiac index, were related to the degree of impairment in glomerular filtration.[10–12] Along this line, Damman *et al.* showed in 30 patients with stable chronic HF that following a diuretic withdrawal, a subtle urinary volume increase occurred, paralleling an increase in markers of tubular renal injury.[13] CA125, a glycoprotein released by mesothelial cells in response to a mechanical or inflammatory stimulus, has been shown to be a reliable marker of systemic congestion.[15–18] In fact, serum levels of this glycoprotein were significantly related to the presence of mesothelial effusion and peripheral oedema, independent of age, gender, and renal function.[17] Interestingly, CA125 provided additional prognostic information beyond natriuretic peptides.[17] In addition, other factors such as wide availability, low cost, standardized measurement, and long half-life support the use of this biomarker in routine clinical practice.[16–18]

In this study, conciliating both previous pathophysiological postulates, we found that the high mortality risk associated with the use of HDLDs is strongly dependent on levels of BUN and serum CA125. We found that in patients with CA125 <35 U/mL (no important fluid overload), HDLDs were associated with high mortality in patients with BUN above the median (C1), but not in those with BUN below the median (C2), reproducing the results recently published by Testani *et al.*[9] in patients with stable chronic HF, a scenario where the majority of patients exhibit normal CA125 values.[18] Thus, in the absence of important fluid overload, higher BUN levels may help to identify those patients in which the potentially beneficial effect of HDLD does not produce the potentially deleterious effect on renal function and/or neurohormonal activation.

Conversely, in patients with CA125 $\geq$ 35 U/mL, the direction of the association mediated by BUN levels was divergent. Indeed, the use of HDLDs in patients with high BUN (C4) was associated with improved survival, while in those with low BUN it was associated with higher mortality (C3). Based on previous experimental studies where selective congestion of the renal veins induced an increase in neurohormonal parameters,[31,32] we speculate that the survival benefit associated with the use of HDLD suggests that renal dysfunction/neurohormonal activation largely depends on venous

Table 3 Multivariable regression estimates indicating the effect of high-dose loop diuretics on all-cause and cardiovascular mortality, according to carbohydrate antigen 125–blood urea nitrogen, carbohydrate antigen 125–creatinine, and carbohydrate antigen 125–estimated glomerular filtration rate categories

Dual-marker variables	Hazard ratio (95% CIs)	*P*-value	Harrell C-statistic	Omnibus *P*-value
All-cause mortality				
CA125 categories–BUN categories[a]	HDLDs			
C1	2.29 (1.51–3.46)	0.000	0.770	<0.001
C2	1.22 (0.73–2.04)	0.448		
C3	1.94 (1.36–2.76)	0.000		
C4	0.73 (0.55–0.98)	0.034		
CA125–eGFR[b]	HDLDs			
C1	2.41 (1.40–4.14)	0.002	0.741	<0.001
C2	1.67 (1.12–2.48)	0.011		
C3	1.46 (1.11–1.92)	0.007		
C4	0.76 (0.54–1.09)	0.135		
CV mortality				
CA125 categories–BUN categories[a]	HDLDs			
C1	2.42 (1.54–3.78)	0.000	0.7535	0.003
C2	0.95 (0.51–1.75)	0.861		
C3	1.21 (0.75–1.95)	0.432		
C4	0.86 (0.61–1.20)	0.366		

BUN, blood urea nitrogen; CA125, serum carbohydrate antigen 125; eGFR, estimated glomerular filtration rate; HDLD, high-dose loop diuretics (furosemide equivalent doses ≥120 mg/day).
[a]CA125 and BUN categories: C1, CA125 ≤35 U/mL and BUN above the median; C2, CA125 ≤35 U/mL and BUN below the median; C3, CA125 >35 U/mL and BUN below the median; C4, CA125 >35 U/mL and BUN above the median.
[b]CA125 and eGFR: C1, CA125 ≤35 U/mL and eGFR <45 mL/min/m^2; C2, CA125 ≤35 U/mL and eGFR ≥ 45 mL/min/m^2; C3, CA125 >35 U/mL and eGFR ≥45 mL/min/m^2; C4, CA125 >35 U/mL and eGFR <45 mL/min/m^2.

congestion in C4 patients, a situation where an aggressive decongestion would result in a net positive prognostic effect.

Finally, CA125 >35 U/mL and BUN below the median (C3) may help to identify those patients with fluid overload or tissue redistribution where renal venous congestion is not important, a situation where an adequate diuretic response would be expected following the first weeks after hospitalization. Based on a previous result showing that CA125 undergoes important modifications following the first weeks after discharge (especially for those with high values during hospitalization),[18] we speculate that the excess risk associated with the use of HDLDs in this category (high CA125 in the absence of renal dysfunction/neurohormonal activation) stems from the fact that most of these patients would control fluid overload within the first weeks following discharge (normalizing CA125 values) and, therefore, move either to C2 (normal CA125 and BUN) or to C1 (normal CA125 but elevated BUN).

Our findings underscore the importance of including a surrogate for systemic/pulmonary congestion as part of the equation relating HDLDs to mortality. Indeed, we believe that this hypothesis-generating study constitutes a first step to delineate further clinical research lines in order to: (i) select those patients who benefit from the use of HDLDs; and (ii) carefully titrate the intensity of diuretic therapy for those patients deemed at risk for their deleterious effects. A clinical instrument able to perform these two tasks represents an unmet need in the management of patients discharged after an episode of AHF, a situation where a residual fluid overload may still be present.[14]

Limitations

Given the observational nature of this study, the contamination of our results due to confounding by indication cannot be excluded. Furthermore, the fact that the treating physicians were not blinded to the value of these markers makes this study prone to channelling bias, even in the absence of specific recommendations about the use of CA125 and BUN for guiding patient therapy. In order to minimize such unintentional influences, and within the available resources, we developed a well-adjusted multivariable model by including the most important predictors of mortality in AHF using a state of the art survival methodology.[21] Is also worth mentioning the possibility that the sample size may have been insufficient to test the interaction effects with appropriate statistical power. We have assumed throughout the study that CA125 is a reliable surrogate for fluid overload, and also renal venous congestion, a presumption that needs to be corroborated with carefully designed experimental studies. BUN values are influenced by prior administration of HDLDs and other factors such as protein catabolism and diet, factors that were not accounted for in this study and might act as important confounders. Furthermore, the lack of serial measurements and the temporal dissociation

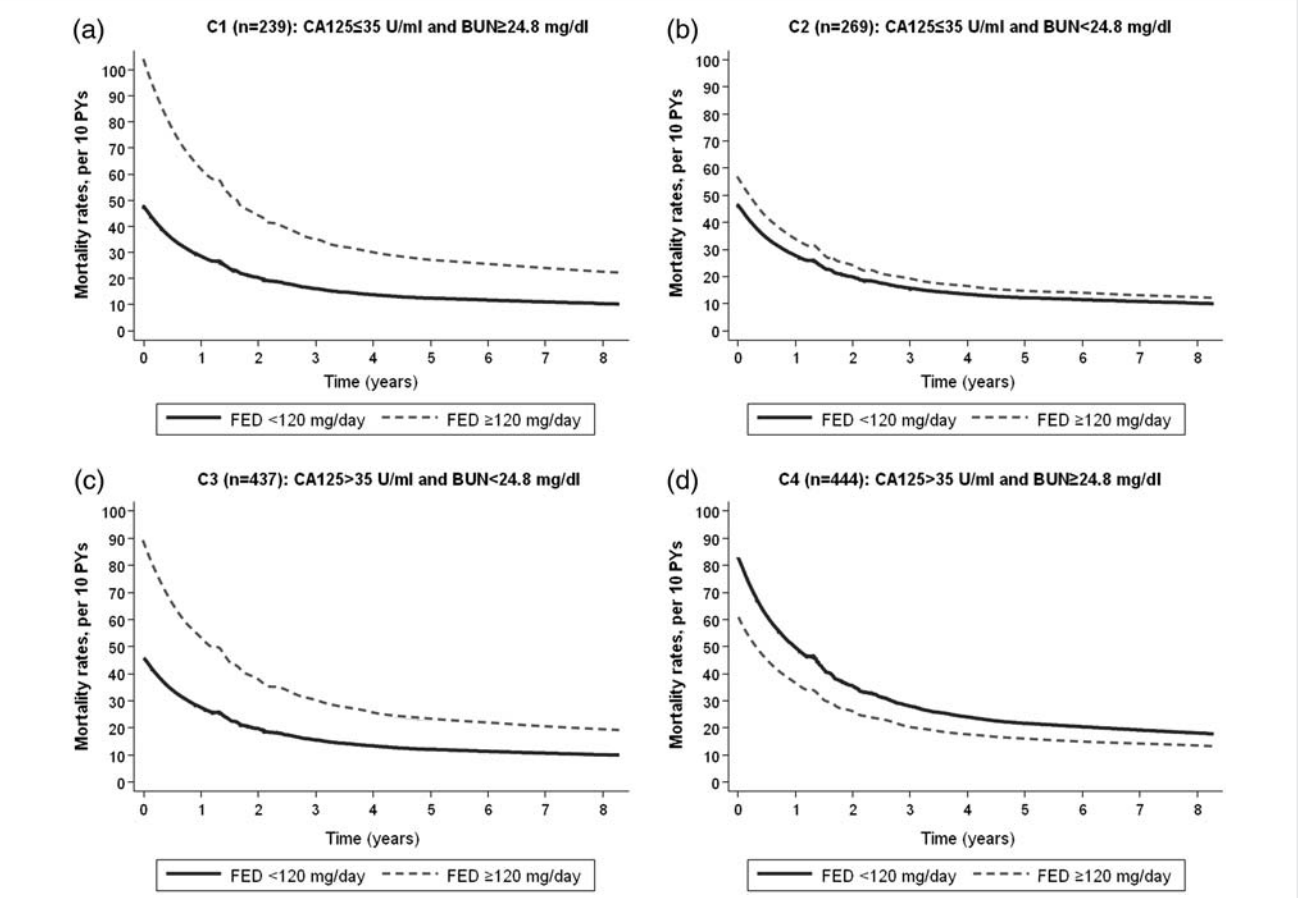

Figure 2 Mortality rates (expressed as 10 PYs) estimated for patients with and without high-dose loop diuretics at each BUN–CA125 category, and plotted against follow-up time. BUN, blood urea nitrogen; CA125, carbohydrate antigen 125; FED, furosemide equivalent dose; PYs, person-years.

between the variables precludes evaluating the updated effect of FED, BUN, and CA125 on mortality. Finally, we cannot unravel the complex mechanisms underlying these results.

Conclusions

Following a hospital discharge for AHF, the higher mortality risk associated with the use of HDLDs appears to be dependent on levels of CA125 and BUN. In patients with normal CA125, HDLD use was associated with higher mortality if BUN was above the median but not in those where it was below the median. Conversely, in patients with high CA125, the direction of the association mediated by BUN levels was the opposite (the HDLD group showed an association with increased survival if BUN was above the median, but an association with increased mortality in those with BUN below the median). Further studies are needed to corroborate our results and to provide robust experimental evidence about the complex association between HDLD dose, renal function, systemic congestion, neurohormonal activation, and subsequent mortality.

Supplementary material

Supplementary material is available at *European Journal of Heart Failure* online.

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