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CA125-Guided Diuretic Treatment Versus Usual Care in Patients With Acute Heart Failure and Renal Dysfunction

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ABSTRACT

BACKGROUND: The optimal diuretic treatment strategy for patients with acute heart failure and renal dysfunction remains unclear. Plasma carbohydrate antigen 125 (CA125) is a surrogate of fluid overload and a potentially valuable tool for guiding decongestion therapy. The aim of this study was to determine if a CA125-guided diuretic strategy is superior to usual care in terms of short-term renal function in patients with acute heart failure and renal dysfunction at presentation.

METHODS: This multicenter, open-label study randomized 160 patients with acute heart failure and renal dysfunction into 2 groups (1:1). Loop diuretics doses were established according to CA125 levels in the CA125-guided group (n = 79) and in clinical evaluation in the usual-care group (n = 81). Changes in estimated glomerular filtration rate (eGFR) at 72 and 24 hours were the co-primary endpoints, respectively.

RESULTS: The mean age was 78 ± 8 years, the median amino-terminal pro-brain natriuretic peptide was 7765 pg/mL, and the mean eGFR was 33.7 ± 11.3 mL/min/1.73m^2. Over 72 hours, the CA125-guided group received higher furosemide equivalent dose compared to usual care ($P = 0.011$), which translated into higher urine volume ($P = 0.042$). Moreover, patients in the active arm with CA125 >35 U/mL received the highest furosemide equivalent dose ($P < 0.001$) and had higher diuresis ($P = 0.013$). At 72 hours, eGFR (mL/min/1.73m^2) significantly improved in the CA125-guided group (37.5 vs 34.8, $P = 0.036$), with no significant changes at 24 hours (35.8 vs 39.5, $P = 0.391$).

CONCLUSION: A CA125-guided diuretic strategy significantly improved eGFR and other renal function parameters at 72 hours in patients with acute heart failure and renal dysfunction.

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KEYWORDS: Acute heart failure; Biomarker guided-therapy; Carbohydrate antigen 125; Clinical trial; Diuretic treatment; Renal failure

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INTRODUCTION

The optimal diuretic strategy in patients with acute heart failure remains unclear,[1,2] particularly when renal dysfunction coexists at presentation.[2,3] Overwhelming evidence indicates that the coexistence of these 2 conditions is associated to longer hospital stays and higher risk of adverse clinical outcomes.[4]

Recent studies indicated that the prognostic implications of worsening renal function are strongly related to clinical response, volume status, magnitude of changes in renal function, and degree of baseline renal impairment.[3-6] Recent studies have highlighted the potential contribution of renal venous congestion to renal impairment[3,7] beside the putative effect of renal hypoperfusion. Unfortunately, traditional methods of evaluation have limited accuracy in terms of assessing the severity and organ distribution of fluid overload. Indeed, no clinical tool in the routine patient management can identify whether renal hypoperfusion or renal venous congestion play a major role in the pathogenesis of renal dysfunction in acute heart failure.[8]

CLINICAL SIGNIFICANCE

- At 72 hours, the CA125-guided strategy group had a higher dose of loop diuretics and higher urine volume than in usual-care protocols.
- At 72 hours, the CA125-guided strategy group showed more improved renal function than patients in usual-care protocols.
- The CA125-guided strategy derived in significant reductions in clinical events at 30 days.
- Our data support CA125 to adjust diuretics dose in acute heart failure with renal dysfunction.

Carbohydrate antigen 125 (CA125) has emerged as a reliable marker of congestion in patients with acute heart failure.[9] Indeed, a recent clinical trial showed that, compared to usual care, CA125-guided therapy was associated with a marked reduction in the composite endpoint of 1-year death or acute heart failure-related readmission in acute heart failure. The improvement in prognosis was mainly the effect of individualizing patients' decongestive therapy.[10] However, CHANCE-HF design did not address the role of worsening renal function in the outcomes tested. Preliminary observational data suggest that plasma levels of CA125 may play a role for tailoring the intensity of diuretic treatment in patients with acute heart failure and renal dysfunction on admission by identifying the congestive renal failure phenotype.[11] Specifically, in patients with acute heart failure, we found that higher doses of diuretics translated into lower adverse events and short-term improvement in renal function in those with higher values of CA125 and renal dysfunction on admission. At the opposite, in those with low CA125 and renal dysfunction on admission, higher diuretic doses were associated with higher risk of adverse clinical events and further worsening renal function.[11]

In this trial, we hypothesize CA125 diuretic-guided treatment compared with standard of care will improve short-term renal and clinical outcomes in patients with acute heart failure and renal dysfunction at presentation, a subset of patients known to be at higher risk of adverse events and in which the intensity of depletive treatment is even more uncertain.[1,2]

METHODS

Study Design

This investigator-initiated, multicenter, open-label, parallel study, randomized patients with acute heart failure and renal dysfunction at presentation in 2 groups (1:1). One group received usual care (ie, regular loop diuretics with dosage based on clinical evaluation and no knowledge of CA125 values). The other group received loop diuretics with dosage based on plasma levels of CA125 (CA125 guided).[12] Due to the study design, physicians were not blinded to patient allocation. All other personnel and patients involved in the study were blinded. Total loop diuretic dose (mg/d) was converted to furosemide equivalent dose following the equation used by Levy et al.[13] The conversion used was furosemide 80 mg = torsemide 40 mg = hydrochlorothiazide 25 mg. Hydrochlorothiazide contributed only when added to loop diuretics.

The study was conducted in accordance with the principles of the Declaration of Helsinki, with the ICH Guidelines for Good Clinical Practice, and it fully conformed to national regulations. The protocol, the informed consent form, the participant information sheet, and all applicable documents were approved by the appropriate Ethics Committee (*Comite de Ética del Hospital Clínico Universitario de Valencia*) and by the *Agencia Española del Medicamento y Productos Sanitarios* [AEMPS]). All patients signed written informed consent. All analyses were performed by an independent company (MedStats Consulting, Reading, PA, USA). This study was registered with ClinicalTrials.gov Identifier: NCT02643147.

Study Population

The study population included patients with acute heart failure and renal dysfunction at presentation who required either hospital admission or ambulatory intravenous diuretic administration for at least 72 hours, based on the severity of their symptoms. The inclusion and exclusion criteria were published previously[12] and are presented in Table 1. The number of patients with acute heart failure that were enrolled and managed in an ambulatory setting was 21 (11 in the usual care and 10 in the active arm, $P = 0.863$).

Study Procedures

Screening and Eligibility Assessment (Visit 0). As soon as the diagnosis of acute heart failure was confirmed, patients were screened and randomized within the first

Table 1 Inclusion and Exclusion Criteria

Inclusion criteria	Exclusion criteria
• Presence of symptoms (dyspnea at rest or minimal exertion) or signs attributable to congestion (signs of congestion on chest radiography or presence of peripheral edema or ascites or jugular engorgement to 45° or crackles on lung auscultation) • NT-proBNP >1000 pg/mL or BNP >100 pg/mL at presentation • Serum creatinine ≥1.4 mg/dL on admission, with eGFR <60 mL/min/1.73m^2 • Intention to be treated with intravenous loop diuretics • Participant or his legal representative is willing and able to give informed consent for participation in the study	• Life expectancy <6 months due to other comorbid conditions • Cardiogenic shock • Diagnosis of ACS in the previous 30 days • Pregnancy at the time of inclusion • Severe obstructive or restrictive lung disease • Previously known stage V CKD (eGFR <15 mL/min/1.73m^2) or patient included in the dialysis program • Participation in another randomized trial at the time of inclusion • History of malignancy within the last 2 years • Temperature ≥38°C or diagnosis of pneumonia

ACS = acute coronary syndrome; BNP = brain natriuretic peptide; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; NT-proBNP = amino-terminal pro-brain natriuretic peptide.

24 hours. Screening included signing and dating the informed consent form; review of the inclusion and exclusion criteria; collection of demographic data; a complete medical history, including current treatment and medications taken within the last 30 days; New York Heart Association (NYHA) functional class evaluation; dyspnea assessment, measured using a visual analogue scale; recording of vital signs; a complete physical examination; electrocardiogram; blood tests, including hematology and chemistry (sodium, potassium, parameters of renal function, CA125, amino-terminal pro-brain natriuretic peptide [NT-proBNP], and high-sensitivity troponin T [hs-TnT] serum levels); and urine electrolyte determination. Mean time from admission to randomization was 6 ± 3 hours. Median (interquartile range [IQR]) dose of intravenous furosemide before randomization was 40 (20) mg.

Follow-up Visits (24 Hours, 72 Hours, and 30 Days). Scheduled follow-up visits were performed at 24 hours, 72 hours, and 30 days after randomization (final visit). These visits included vital signs, complete physical examination, functional class evaluation (NYHA), dyspnea assessment (visual analogue scale), diuresis volume (24 and 72 hours), and collection of blood and urine samples. During the study period, all concomitant medications and clinical adverse events (death from all causes or new worsening of acute heart failure) were recorded. Postdischarge visits outside this preplanned schedule (optional visits) were permitted at discretion of the physician in charge of the patient.

Trial Intervention

Eligible patients were randomized to receive intravenous diuretics with the dosage based on either conventional clinical evaluation (usual care) or based on a CA125 values. Supplementary Table 1 (available online) summarizes the strategies used to determine treatment for the 2 groups. CA125 was available to the physician in charge of patient only in the CA125-guided arm. To mitigate sources of variability, each patient had the same physician along the trial. Other personnel involved in the study was blinded to treatment allocation. At the end of the study, the CA125 levels were unblinded for all patients. Given the prolonged half-life of CA125, no serial measurement of CA125 were obtained by protocol during the first 72 hours.[9]

Usual Care Strategy

The initial diuretic strategy was based on the presence of symptoms and signs of systemic congestion and on current guideline recommendations.[1,14] The study protocol advised maintaining the starting dose for at least the first 24 hours. Maintenance or later revision of the diuretic dose was based on clinical (symptoms and signs of fluid overload) or laboratory criteria.

CA125-Guided Strategy

Patients With CA125 ≤35 U/mL. An initial dose of intravenous furosemide ≤80 mg/d was recommended regardless of the previous dose of loop diuretics. As for usual care, the study protocol advised maintaining the starting dose for at least the first 24 hours. The removal of oral thiazides or chlorthalidone was also recommended. The decision to modify the initial dose or route of administration of diuretics after the first 24 hours was up to the attending physician and based on patient's clinical and biochemical data.

Patients With CA125 >35 U/mL. The strategy recommended an initial dose of intravenous furosemide >120 mg/d or 2.5 times the oral dose of furosemide that the patient was taking. In cases with striking elevation of CA125 (>100 U/mL) or with concomitant unequivocal clinical signs of systemic congestion, a furosemide dose >160 mg/d was recommended. After 24 hours, diuretic titration, changes in the route of administration, or termination was up to the attending physician based on clinical criteria. Increasing the dose of intravenous furosemide or adding chlorthalidone 25-50 mg/d was recommended if diuresis >3 L during the first 24 hours was not achieved without impaired renal function (>0.5 mg of creatinine relative to baseline).

For both arms of the study, doses of furosemide lower than 250 mg/d were administered as bolus injections, and higher doses were administered via continuous infusion.

We recommended a 2-g sodium diet during trial. The indications for other drugs used in heart failure in both treatment arms were based on recommendations for clinical practice.[1,14]

Endpoints

Primary Endpoints. The primary endpoint was defined as the comparison among the 2 arms in absolute changes in estimated glomerular filtration rate (eGFR; Modification in Diet in Renal Disease-MDRD-4 formula) at 72 hours after randomization. Changes evaluated at 24 hours were considered a co-primary endpoint.

Secondary Endpoints. The following comparisons were defined as secondary endpoints: 1) absolute changes in eGFR at 30 days; 2) changes in serum creatinine at 24, 72 hours, and 30 days; 3) changes in serum blood urea nitrogen at 24, 72 hours, and 30 days; 4) change in NYHA functional class at 24, 72 hours, and 30 days; 5) dyspnea assessment on visual analogue scale (score of 0 corresponds to the patient's subjective feeling of "worst breathing" and a dyspnea visual analogue scale score of 100 corresponds to "best breathing") at 24 and 72 hours; 6) changes in plasma levels of NT-proBNP and hs-TnT at 72 hours; and 7) incidence of adverse clinical outcomes measured by a composite of death or hospitalization for acute heart failure during the 30-day trial duration.

Exploratory Endpoints

Within an exploratory framework, we sought to determine if the 2 treatment groups differed in the proportion of worsening renal failure (an increase in creatinine ≥0.3 mg/dL or a decrease in eGFR >20%) and improvement in renal function (a decrease in creatinine ≥0.3 mg/dL or an increase in eGFR ≥20%).

Safety Assessment

During the duration of the trial, we followed a strict safety surveillance policy in aspects related to patient's dehydration and electrolyte disturbances such as hyperkalemia and hypokalemia.

Sample Size

Assuming an alpha of 0.05, a power of 0.80, and an effect size of 0.19 in the difference of improvement in renal function proportion, the estimated sample size was 77 patients in each group (total 154 patients). Assuming a loss of 5% to 10% of patients (consent withdrawn, lost to follow-up at 30 days, and early deaths), the proposed sample size was increased by 10% (final = 170 patients). The effect size of interest was obtained from our hospital acute heart failure registry.

Statistical Analysis

All randomized patients were analyzed in the treatment group in which they were originally allocated (intention-to-treat analysis). A detailed description of the sample size calculation is presented elsewhere.[12]

Continuous baseline characteristics among the 2 arms are reported as mean/standard deviation (SD) or median/IQR and compared with *t* tests or rank sum tests as appropriate. For categorical variables, frequencies (percentages) and chi-square test were used.

Treatment differences in absolute changes of continuous outcomes were tested using linear mixed regression analysis (LMRA) with unstructured covariance, and the variable visit (24 hours, 72 hours, and 30 days) as random coefficient. Results were presented as least squares means (LSM) with 95% confidence intervals (CIs). All LMRA models included as covariates the pretreatment values of the outcome, CA125, prior baseline history of renal insufficiency, and recruiting center—the latter included as cluster variable—to account for potential autocorrelations among observations within each center. Differences in binary outcomes were tested using generalized linear mixed models (GLMMs) and results were presented as predicted probabilities. The effect of treatment on the composite endpoint of death or rehospitalization for acute heart failure was evaluated at 30 days using stratified (by center) log-rank test. Differences in survival probabilities were depicted with a Kaplan-Meier plot. The hazard ratios (HRs) and 95% CIs were estimated with Cox proportional regression using center as a stratification factor.

A 2-sided P value <0.05 was considered statistically significant for all analyses. All analyses were performed with Stata 15.1.

Results

Patients. A total of 160 patients were included in this study between March 2015 and December 2016 at 9 centers in Spain. Of the 160 patients, 79 were randomly assigned to the CA125-guided therapy group and 81 to the usual care group (Figure 1). The mean age of the study population was 78 ± 8 years, 66.9% were males, 53.1% had left ventricular ejection fraction (LVEF) ≥50%, and the median NT-proBNP level was 7765 (3526-15369) pg/mL. Due to the inclusion criteria, all patients had renal dysfunction on admission, with mean eGFR, creatinine, and blood urea nitrogen (BUN) levels of 33.7 ± 11.3 mL/min/1.73m^2, 1.98 ± 0.52 mg/dL, and 47.1 ± 16.8 mg/dL, respectively. A total of 43.7% of patients had eGFR <30 mL/min/1.73 m^2.

The baseline characteristics of patients in the 2 treatment groups are shown in Table 2. Overall, groups were well balanced after randomization except that the usual-care group had a higher proportion of prior myocardial infarction and left bundle branch block. Of note, there were no differences in the use of loop diuretics before decompensation and the proportion of patients with CA125 >35 U/mL was higher

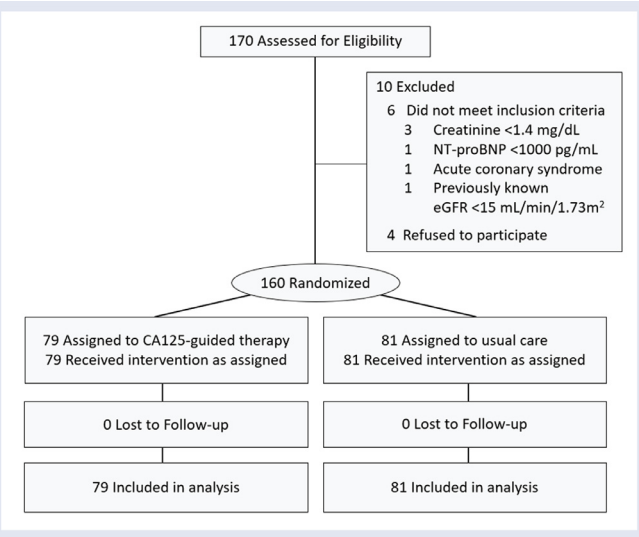

Figure 1 Flow chart. CA125 = carbohydrate antigen 125; eGFR = estimated glomerular filtration rate; NT-proBNP =amino-terminal pro-brain natriuretic peptide.

than 60% in both groups (Table 2). Likewise, the baseline risk profile did not significantly differ between patients who were hospitalized and those treated ambulatory (Supplementary Table 2, online).

Diuretic Treatment and Urine Volume in the Treatment Groups

All patients received intravenous furosemide for a median (IQR) of 4 days (4-7). Over the course of 72 hours, the CA125-guided treatment group had a higher median (IQR) total dose of furosemide equivalent dose (FED_{72h}) compared to the usual-care strategy group [480 mg (260-730) vs 320 mg (240-500); $P = 0.011$] as well as higher urine volume ($Diuresis_{72h}$) [6750 mL (5550-8300) vs 6300 mL (4600-7500); $P = 0.029$]. There was a trend toward a higher prescription of thiazides during decompensation in the active arm (26.6% vs 14.8, $P = 0.066$) (Supplementary Table 3, online). After stratifying FED_{72h} and $Diuresis_{72h}$ by treatment group and CA125 status, patients in the active arm with CA125 >35 U/mL had the highest FED_{72h} values, while those with CA125 ≤35 U/mL had the lowest values (Figure 2A, omnibus P value <0.001). $Diuresis_{72h}$ was also greatest (7750 mL) in the subgroup of patients in the active arm with CA125 >35 U/mL (Figure 2B, omnibus P value = 0.013). There were no differences of in-hospital treatments with angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), betablockers, aldosterone antagonists, nitrates, and dopamine (Supplementary Table 3). The median number of visits across both strategies was also similar (Supplementary Table 3). In the group of patients randomized at hospital admission, the median (IQR) length of stay was lower in CA125-guided arm [7 (3) vs 8 (3), $P = 0.025$]."

Diuretic Strategies and Renal Function Parameters

Continuous Renal Marker Outcomes. At 24 hours there were no significant changes in eGFR between both strategies (Figure 3A). However, at 72 hours, patients in the CA125-guided arm showed a significant improvement in eGFR: an increase of 2.8 mL/min/1.73m^2, 95% CI = 0.14-5.40; $P = 0.036$. At 30 days, patients belonging to the active arm remained showing higher eGFR (Figure 3A).

Overall, similar findings applied to other renal function markers. At 24 hours, no significant differences were found in creatinine and BUN, but then again at 72 hours, patients in the CA125-guided arm showed lower creatinine and BUN (Figure 3B and 3C). At 30 days, there was a decrease in creatinine (Figure 3B) and BUN (Figure 3C), changes that did not achieve statistical significance.

Binary Renal Marker Outcomes. There were no significant differences across both treatment strategies (CA125-guided therapy vs usual care) regarding the risk of worsening renal function or improvement in renal function at 24 (2.3% vs 3.3%, $P = 0.742$, and 6.0 % vs 4.8%, $P = 0.940$, respectively) and 72 hours (10.3% vs 15.3%, $P = 0.707$, and 30.4% vs 23.6%, $P = 0.180$, respectively). However, at 1 month, the CA125-guided group showed an increased probability of improvement in renal function (35.7% vs 22.2%, $P = 0.003$) without differences in worsening renal function (30.5% vs 39.4%, $P = 0.529$).

Effect of Diuretic Strategies and Other Endpoints

NYHA: CA125-guided strategy was associated to a reduction in the probability of being in NYHA class III/IV at 72 hours (Table 3).

Visual analogue scale: At 24 hours, the visual analogue scale was significantly better in the active arm (55.49% vs 52.14%, P <0.001). At 72 hours and 30 days, no statistically significant differences were found, despite the direction of the effect always favor the CA125-guided strategy (Table 3).

NT-proBNP and hs-TnT: There were no differences in NT-proBNP and hs-TnT levels at 72 hours among the 2 treatment groups (Table 3).

Clinical events: At 30 days, 27 (16.9%) composite events of all-cause death (n = 12) or heart failure-related hospitalization (n = 16) were registered. Cox regression analysis showed that patients in the CA125-guided arm showed a statistical trend to lower risk of the composite endpoint (HR = 0.46, 95% CI: 0.21-1.03; $P = 0.059$). Kaplan-Meier curves are shown in Supplementary Table 4 (online).

Safety Criteria

There were no significant differences in serum potassium levels between the 2 groups either at 24 hours (4.29 ± 0.07 mEq/L in the usual-care group vs 4.16 ± 0.06 mEq/L

Table 2 Baseline Characteristics

Variables	Usual care (n = 81)	CA125-guided therapy (n = 79)	*P* Value
Demographics and medical history			
Age, years	79 ± 8	77 ± 7	0.282
Male, n (%)	55 (67.9)	52 (65.8)	0.780
Hypertension, n (%)	73 (90.1)	71 (89.9)	0.958
DM, n (%)	45 (55.6)	45 (57.0)	0.858
Insulin-dependent DM, n (%)	22 (42.3)	25 (47.2)	0.616
Smoker, n (%)	25 (30.9)	25 (31.6)	0.915
Former smoker, n (%)	4 (4.9)	4 (5.1)	0.971
First admission for AHF, n (%)	28 (34.6)	29 (36.7)	0.777
Prior myocardial infarction, n (%)	31 (38.3)	18 (22.8)	0.034
History of atrial fibrillation, n (%)	38 (46.9)	48 (60.8)	0.079
Stroke, n (%)	10 (12.3)	9 (11.4)	0.852
Peripheral artery disease, n (%)	5 (6.2)	8 (10.1)	0.360
Prior history of renal dysfunction, n (%)	49 (60.5)	57 (72.2)	0.119
Medical devices			
Pacemaker, n (%)	19 (23.5)	13 (16.5)	0.268
ICD, n (%)	18 (22.2)	15 (19.0)	0.613
Clinical presentation			
VAS score	45 ± 19	46 ± 15	0.940
NYHA functional class, n (%)			0.225
II	3 (3.7)	0 (0)	
III	42 (51.9)	43 (54.4)	
IV	36 (44.4)	36 (45.6)	
Peripheral edema, n (%)			0.436
No	18 (22.2)	15 (19.0)	
1-2	40 (49.4)	34 (43.0)	
3-4	23 (28.4)	30 (38.0)	
Vital signs			
Heart rate, bpm	76 ± 17	75 ± 19	0.660
Systolic blood pressure, mm Hg	127 ± 23	127 ± 24	0.932
Diastolic blood pressure, mm Hg	67 ± 12	67 ± 14	0.970
Electrocardiogram and echocardiography			
QRS duration, msec	123 ± 34	120 ± 32	0.547
LBBB, n (%)	17 (21.0)	8 (10.1)	0.059
LVEF, %	47 ± 14	49 ± 15	0.391
LVEF categories, n (%)			0.367
≤40%	31 (38.3)	29 (36.7)	
41-49%	10 (12.3)	5 (6.3)	
≥50%	40 (49.4)	45 (57.0)	
Laboratory results			
Hemoglobin, g/dL	11.7 ± 1.8	11.8 ± 2.0	0.691
Hematocrit, %	36.3 ± 5.4	36.8 ± 5.5	0.547
Anemia (WHO criteria), n (%)	59 (72.8)	56 (70.9)	0.783
Anemia (CDC criteria), n (%)	63 (77.8)	60 (75.9)	0.784
Serum sodium, mEq/L	139 ± 4	139 ± 5	0.272
Serum potassium, mg/dL	4.4 ± 0.6	4.5 ± 0.6	0.284
BUN, mg/dL	46.6 ± 16.0	48.0 ± 17.6	0.594
Creatinine, mg/dL	1.91 ± 0.45	2.04 ± 0.57	0.095
eGFR, mL/min/1.73m^2	33.5 ± 11.3	33.9 ± 11.4	0.820
CA125*, U/mL	58 (23, 110)	55 (22, 114)	0.575
CA125 >35 U/mL, n (%)	54 (66.7)	49 (62.0)	0.540
NT-proBNP*, pg/mL	7997 (4003, 16042)	7393 (3375, 13218)	0.518
Medications received before decompensation			
Loop diuretics, n (%)	72 (88.9)	73 (92.4)	0.446
FED*, mg/d	80 (60, 120)	80 (60, 120)	0.721
Thiazides, n (%)	19 (23.5)	19 (24.1)	0.930

Table 2 (*Continued*)

Variables	Usual care (n = 81)	CA125-guided therapy (n = 79)	*P* Value
Betablockers, n (%)	60 (74.1)	56 (70.9)	0.652
ACEI, n (%)	19 (23.5)	15 (19.0)	0.490
ARB, n (%)	26 (32.1)	18 (22.8)	0.187
MRA, n (%)	32 (39.5)	32 (40.5)	0.897
Statins, n (%)	58 (71.6)	54 (68.4)	0.654

ACEI = angiotensin converting enzyme inhibitors; AHF = acute heart failure; ARB = angiotensin II receptor blockers; BUN = blood urea nitrogen; CA125 = antigen carbohydrate 125; CDC = Centers for Disease Control and Prevention; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; FED = furosemide equivalent dose; ICD = implantable cardioverter-defibrillator; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; MRA = mineral corticoid receptor antagonist; NT-proBNP = amino-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; VAS= Visual Analogue Scale; WHO = World Health Organization.

Continuous variables are expressed as mean ± standard deviation, unless otherwise specified.

*Values expressed as median (interquartile range).

in the CA125-guided group, $P = 0.195$) or at 72 hours (4.12 ± 0.06 mEq/L in the usual-care group vs 4.08 ± 0.06 mEq/L in the CA125-guided group; $P = 0.603$). Furthermore, no statistical significance was achieved when comparing the proportion of hypo (<3.5 mEq/L) and hyperkalemia (>5.0 mEq/L) among the treatment groups (Supplementary Table 5, online).

DISCUSSION

In acute heart failure, renal dysfunction at presentation is highly prevalent and associated with adverse outcomes.[3,4] The use of intravenous loop diuretics remains the cornerstone of treatment for acute heart failure syndromes; however, its dose titration is still determined empirically by a trial-and-error process.[1] The uncertainty about the optimal dose of diuretics is even more important when there is concomitant renal dysfunction at presentation.[1,3] This unmet need prompted us to compare a clinically guided "usual-care" treatment with a CA125-guided strategy. As expected, we found the CA125-guided strategy resulted in a more aggressive and higher variation in doses of loop diuretics. CA125-guided diuretic therapy did not have effect on renal function at 24 hours. At 72 hours, this strategy modestly improved eGFR. However, and despite the modest improvement in renal function status, this strategy

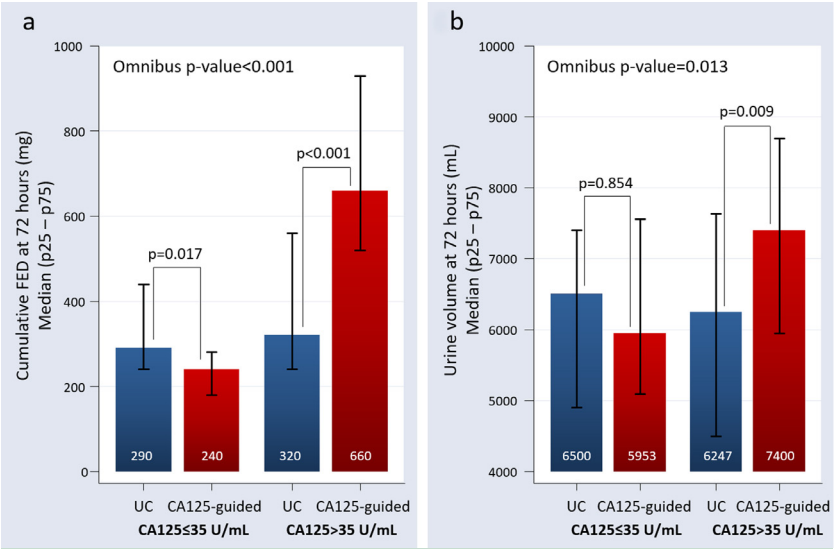

Figure 2 Cumulative intravenous furosemide equivalent dose and diuresis volume at 72 hoursfor the indicated treatment groups and CA125 categories. (**A**) Cumulative furosemide equivalent dose at 72 hours (mg/24 h). (**B**) Urine volume at 72 hours (mL). Omnibus *P* value for the interaction between treatment groups (usual care vs CA125 guided) and the baseline binary level of CA125 (≤35 U/mL vs <35 U/mL). CA125 = carbohydrate antigen 125; FED = furosemide equivalent dose.

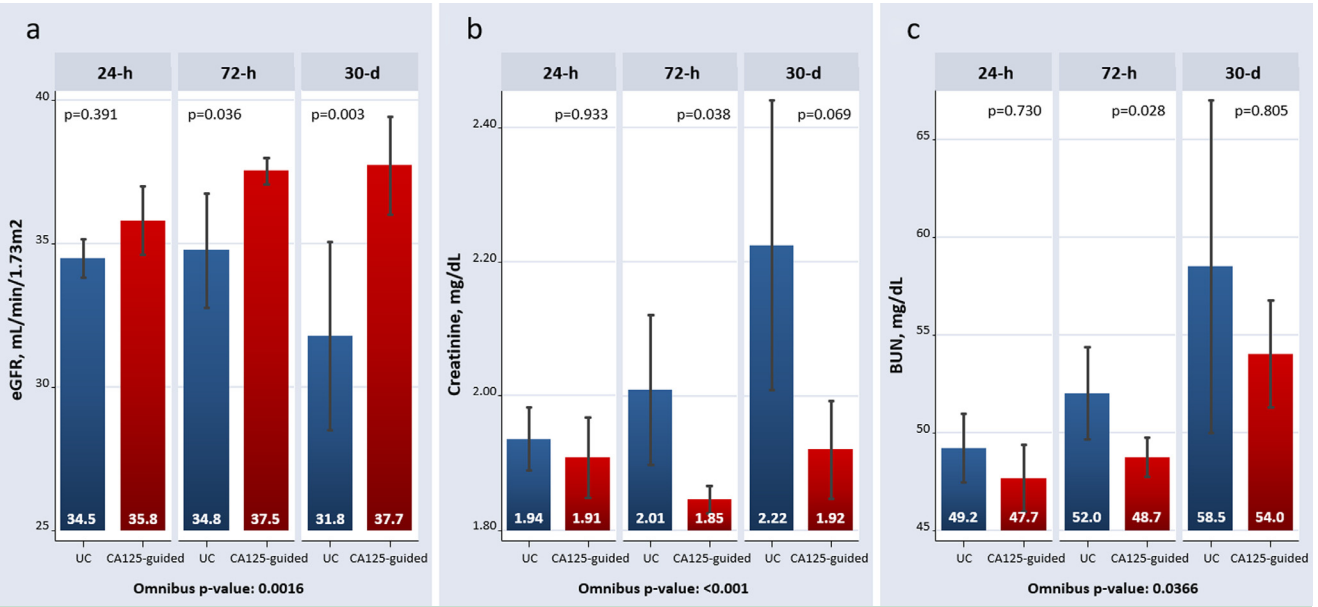

Figure 3 Changes in renal function parameters in the two treatment groups. (**A**) Primary endpoints: eGFR, (**B**) creatinine, and (**C**) BUN. BUN = blood urea nitrogen; CA125 = carbohydrate antigen 125; eGFR = estimated glomerular filtration rate; UC = usual care.

translated into an early improvement of dyspnea and a statistical trend to lower risk of the composite event of death or acute heart failure-admission at 30 days.

Assessment of Fluid Overload: The Role of CA125

Fluid overload is a hallmark of acute heart failure syndromes; however, its severity and distribution are largely heterogeneous.[15,16] Traditional tests for its evaluation have shown limited accuracy.[8,17] Of note, natriuretic peptides have showed lack of correlation with the degree of systemic congestion.[17]

CA125, also called MUC16, is a high molecular weight and extremely complex glycoprotein synthesized by epithelial serous cells.[9] In heart failure, high levels of CA125 were found in two-thirds of patients with acute heart failure and were positively correlated with symptoms or signs of fluid overload, higher atrial and pulmonary pressure, and right ventricular dysfunction.[9,18] Additionally, the trajectory of CA125 levels within the first months of discharge strongly predicts the risk of mortality and readmission following an episode of acute heart failure.[19,20] A recent clinical trial showed that CA125-guided therapy significantly reduced the occurrence of the primary endpoint

Table 3 Diuretic Strategies and Secondary Endpoints

	Usual care	CA125-guided therapy	Δ	95% CI	*P* Value
At 24 hours					
NYHA class III/IV[a,b]	0.66	0.75	0.09	−0.05 to 0.23	0.311
VAS score[a,c]	52.14	55.49	3.35	1.26 to 5.45	<0.001
At 72 hours					
NYHA class III/IV[a,b]	0.49	0.43	−0.06	−0.10 to −0.02	0.003
VAS score[a,c]	57.50	61.25	3.75	−0.16 to 7.67	0.065
Log NT-proBNP[a,c]	8.64	8.65	0.01	−0.11 to 0.14	0.998
Log hsTnT[a,c]	4.12	4.05	−0.07	−0.20 to 0.07	0.534
At 30 days					
NYHA class III/IV[a,b]	0.32	0.23	−0.09	−0.26 to 0.08	0.493
VAS score[a,c]	59.14	63.89	4.75	−1.28 to 10.78	0.169

BUN = blood urea nitrogen; CA125 = antigen carbohydrate 125; CI = confidence interval; eGFR = estimated glomerular filtration rate; hsTNT = high-sensitivity troponin T; IRF = improvement in renal function; NA = not available; NT-proBNP = amino-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; VAS = Visual Analogue Scale; WRF = worsening renal function.

All analysis included recruiting center as cluster variable.

[a]Estimates are adjusted by the baseline value of the marker and an indicator for prior history of renal insufficiency as covariates.

[b]Presented as probability.

[c]Least square means.

(a composite of 1-year all-cause mortality or heart failure −related readmission), the cumulative rate of readmissions (heart failure−related as well as all-cause readmissions), and the number of visits to the emergency department.[10]

The Relevance of Renal Changes in Acute Heart Failure: The Importance of Renal Dysfunction at Presentation. The pathophysiology and clinical relevance of worsening renal function in patients with acute heart failure is complex, multifactorial, and not fully elucidated.[3-5,19,29] In fact, the use of renal function surrogates as a prognostic endpoint in acute heart failure has recently been criticized because a subgroup of patients treated with vigorous diuretic treatment may develop worsening renal function as a result of transient intrarenal physiological changes and hemoconcentration (a surrogate of successful decongestion) rather than true acute kidney injury.[21,22] This criticism is based mostly on findings in patients with normal or mild to moderate renal impairment at presentation and with mild to moderate renal changes during the worsening renal function episode. Indeed, the extrapolation of these findings to patients with more severe renal dysfunction on admission and to those with more dramatic changes is not supported by the current evidence. In fact, we reported previously that the prognostic meaning of renal function changes in patients with acute heart failure on intravenous diuretic therapy depends largely on renal function on admission. In that work, in which we evaluated the prognostic meaning of creatinine changes in hospitalized patients with acute heart failure, we found a positive graded association of increased creatinine with mortality only when renal insufficiency was present on admission.[6] The findings of this trial conciliate both postulates. A more aggressive diuretic therapy guided by CA125 was associated to an improvement in renal function. Thus, in patients with acute heart failure and renal dysfunction on admission, a renal function improvement seems a desirable endpoint. However, the magnitude and timing of these differences in renal markers are not necessarily aligned to the benefits found in clinical status. In this subset of patients, renal function outcomes after CA125-guided treatment, although important, should be evaluated contingent to patient's clinical evolution.

Patients With Acute Heart Failure and Renal Dysfunction: The Same Phenotype for Different Pathophysiological Processes. There is compelling evidence that transitory hemodynamic changes play a pivotal role in the pathogenesis of worsening renal function in patients with acute heart failure; thus, the presence of renal dysfunction on admission may, in a subset of patients, indicate that worsening renal function was already present preadmission.[3,4,7] This subgroup of patients usually exhibits higher fluctuations in renal function changes in response to aggressive depletion treatment.[2,23] Although reduced cardiac output and renal hypoperfusion play an important role, recent evidence highlights the importance of renal congestion (increased intra-abdominal or hydrostatic pressure of the renal vein) in the pathogenesis of worsening renal function in acute heart failure.[3,7,24,25] We believe that the end-result effect on kidney function may represent a balance between these 2 opposing forces. Patients with predominant renal venous congestion are thus likely to respond to an aggressive diuretic strategy with improved renal function despite the confounding effect of hemoconcentration. Conversely, when renal hypoperfusion predominates, an aggressive diuretic strategy is likely to lead to further renal function deterioration. In the present study, the improvement in renal status observed at 72 hours and at 30 days in the CA125-guided arm provided indirect evidence that congestion plays an important role in the pathogenesis of renal dysfunction.

Our findings, although preliminary, support the need for individualized treatment with diuretics in patients with acute heart failure and renal dysfunction. Indeed, recent studies that used a trial-and-error strategy for diuretics' dose titration have failed to show superiority of any diuretic strategy in acute heart failure syndromes,[2,26,27] reinforcing the fact that a one-size-fits-all approach is not a good choice. Indeed, the clinical interpretation of renal changes under vigorous decongestive treatment requires a comprehensive assessment that includes the magnitude of the changes, the baseline renal function, changes in markers of hemoconcentration, and the clinical response.

Beyond these considerations, there are some additional strengths that deserve to be highlighted. In pivotal and recent trials of patients with acute heart failure, those with severe renal dysfunction have been underrepresented.[2,26,27] On the contrary, for this trial we selected patients with acute heart failure and renal dysfunction, a subgroup of patients deemed to be at high risk of adverse events and in which the decongestive treatment is mostly empirical. Second, CA125 is a low-cost and widely available marker, properties that can favor its smooth incorporation in routine clinical practice. And third, CA125 levels are not importantly influenced by common confounders such as age, body mass index, and renal function.[9] This behavior provides advantages over natriuretic peptides, which, based on recent publication, failed to show an important role as a treatment-guiding marker in acute heart failure.[28]

This trial is not exempt of limitations: First, we cannot rule out some operator bias because treatment was not blinded to the physician in charge of the patient. Unfortunately, the information about patients' levels of CA125 was mandatory as a part of the active strategy. Second, because of the limited sample size, some of the negative results could be explained by type II error (insufficient statistical power). This limitation may be playing an important role on the lack of robust evidence supporting the superiority of the CA125-guided strategy on preventing adverse clinical events and on the stratified analyses by CA125 status at baseline. Third, we did not evaluate the effect of both strategies on other surrogates of decongestion such as weight and venous pressures. Fourth, we did not assess fluid intake during the trial, precluding us to evaluate its effect as a confounder on the treatment differences.

Fifth, we did not stratify the randomization process on prior stable chronic renal dysfunction, which make difficult to evaluate the true rate of worsening renal function and the end effect of the treatment on renal markers' changes.

CONCLUSION

In patients with acute heart failure and renal dysfunction at presentation, CA125-guided intravenous diuretic therapy had no effect on eGFR at 24 hours but resulted in better renal performance at 72 hours and 30 days. In addition, with this strategy a borderline reduction of adverse clinical endpoints was also noted at 30 days. This preliminary evidence requires additional and better-powered studies confirming the utility of CA125 for tailoring decongestive treatment in scenarios of acute heart failure.

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SUPPLEMENTARY DATA

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APPENDIX 1. LIST OF INVESTIGATORS OF IMROVE-HF

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Supplementary Table 1 Diuretic Strategies

Conventional strategy	
Loop diuretics dosage according to the presence of symptoms and signs of systemic congestion	
CA125-guided strategy	
CA125 ≤35 U/mL	CA125 >35 U/mL
• Initial dose of intravenous furosemide ≤80 mg/day • Removal of thiazides or chlorthalidone • After 24 h: dose adjustment based on clinical and/or laboratory criteria	• Initial dose of iv furosemide >120 mg/day or 2.5 times the previous oral dose • If CA125 >100 U/mL and/or concomitant unequivocal clinical signs of systemic congestion, doses >160 mg/day • After 24 h: increasing the dose of iv furosemide and/or adding chlorthalidone 25-50 mg/day will be recommended if diuresis <3 L during the first 24 hours

CA125 = carbohydrate antigen 125

Supplementary Table 2 Baseline Characteristics (Hospitalized vs. Ambulatory Setting)

Variables	Hospitalized (n=139)	Ambulatory (n=21)	*P* Value
Treatment intervention			
CA125-guided therapy	69 (49.6)	10 (47.6)	0.863
Demographics and medical history			
Age, years	78 ± 8	77 ± 7	0.454
Male, n (%)	91 (65.5)	16 (76.2)	0.331
Hypertension, n (%)	124 (89.2)	20 (95.2)	0.391
DM, n (%)	78 (56.1)	12 (57.1)	0.929
Insulin-dependent DM, n (%)	40 (44.9)	7 (43.8)	0.930
Smoker, n (%)	40 (28.8)	10 (47.6)	0.083
First admission for AHF, n (%)	55 (39.6)	2 (9.5)	0.007
Prior myocardial infarction, n (%)	40 (28.8)	9 (22.8)	0.192
History of atrial fibrillation, n (%)	74 (53.2)	12 (57.1)	0.738
Stroke, n (%)	19 (13.7)	0	0.071
Peripheral artery disease, n (%)	13 (9.3)	0	0.144
Prior history of renal dysfunction, n (%)	91 (65.5)	15 (71.4)	0.590
Medical devices			
Pacemaker, n (%)	25 (18.0)	7 (33.3)	0.101
ICD, n (%)	27 (19.4)	6 (28.6)	0.334
Clinical presentation			
VAS score	46 ± 17	42 ± 16	0.311
NYHA functional class, n (%)			0.643
II	3 (2.2)	0 (0)	
III	75 (54.0)	10 (47.6)	
IV	61 (43.9)	11 (54.4)	
Peripheral edema, n (%)			0.508
No	28 (20.1)	5 (23.8)	
1-2	66 (47.5)	8 (38.1)	
3-4	45 (32.4)	8 (38.1)	
Vital signs			
Heart rate, bpm	76 ± 18	72 ± 18	0.340
Systolic blood pressure, mmHg	128 ± 23	125 ± 26	0.581
Diastolic blood pressure, mmHg	68 ± 13	63 ± 10	0.173
Electrocardiogram and echocardiography			
QRS duration, msec	122 ± 31	119 ± 46	0.672
LBBB, n (%)	22 (15.8)	3 (14.3)	0.856
LVEF, %	48 ± 15	47 ± 13	0.847
LVEF categories, n (%)			0.270
≤40%	52 (37.4)	8 (38.1)	
41-49%	15 (10.8)	0	
≥50%	72 (51.8)	13 (61.9)	
Laboratory results			
Hemoglobin, g/dL	11.8 ± 1.9	11.0 ± 1.4	0.057
Serum sodium, mEq/L	139 ± 4	138 ± 6	0.240
Serum potassium, mg/dL	4.5 ± 0.6	4.4 ± 0.7	0.387
BUN, mg/dL	46.6 ± 16.0	51.7 ± 21.2	0.194
Creatinine, mg/dL	1.95 ± 0.46	2.14 ± 0.80	0.126
eGFR, mL/min/1.73m^2	34.1 ± 8.3	33.5 ± 10.1	0.781
CA125*, U/mL	54 (22, 110)	70 (41, 128)	0.095
CA125 >35 U/mL, n (%)	86 (61.9)	17 (80.9)	0.089
NT-proBNP*, pg/mL	7620 (3707, 15438)	8080 (2675, 15300	0.793

Supplementary Table 2 (*Continued*)

Variables	Hospitalized (n=139)	Ambulatory (n=21)	*P* Value
Medications received before decompensation			
Loop diuretics, n (%)	125 (89.9)	20 (95.2)	0.436
FED*, mg/day	80 (40, 120)	120 (80, 160)	0.116
Thiazides, n (%)	31 (22.3)	7 (33.3)	0.268
Betablockers, n (%)	98 (70.5)	18 (85.7)	0.146
ACEI/ARB, n (%)	69 (49.6)	8 (38.1)	0.324
MRA, n (%)	47 (33.8)	9 (42.9)	0.418
Statins, n (%)	97 (69.8)	15 (71.4)	0.878

AHF = acute heart failure; ACEI = angiotensin converting enzyme inhibitors; ARB = angiotensin II receptor blockers; BUN = blood urea nitrogen; CA125 = antigen carbohydrate 125; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; FED = furosemide equivalent dose; ICD = implantable cardioverterdefibrillator; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; MRA = mineralcorticoid receptor antagonist; NT-proBNP = amino-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; VAS = Visual Analogue Scale.

Continuous variables are expressed as mean ± standard deviation, unless otherwise specified.

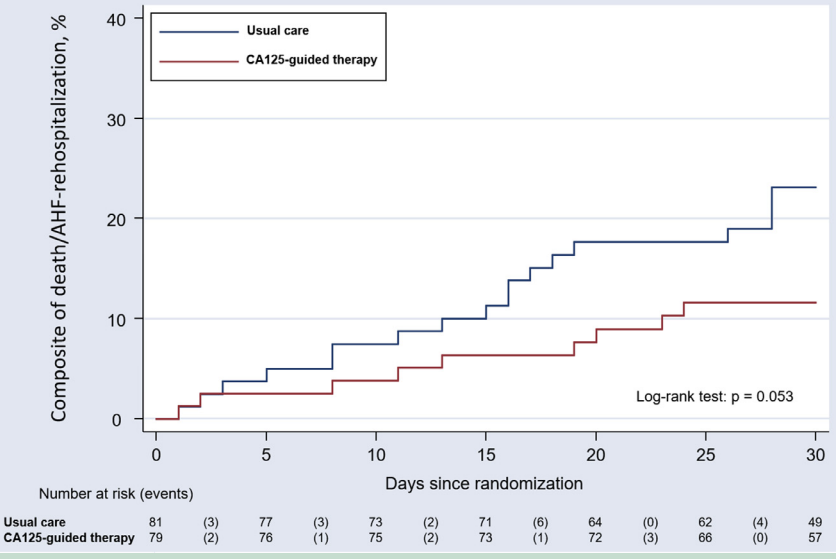
*Values expressed as median (interquartile range).

Supplementary Table 3 Treatment and Visits During the Trial

	Treatments		
Variables	Usual care (n=81)	CA125-guided therapy (n=79)	*P* Value
Intravenous loop diuretics, n (%)	81 (100)	79 (100)	1.000
Accumulated 72h FED, mg/day[a]	320 (240, 500)	480 (260, 730)	0.011
Thiazides, n (%)	12 (14.8)	21 (26.6)	0.066
Betablockers, n (%)	57 (70.4)	52 (65.8)	0.537
ACEI, n (%)	15 (18.5)	12 (15.2)	0.574
ARB, n (%)	21 (25.9)	17 (21.5)	0.513
MRA, n (%)	26 (32.1)	23 (29.1)	0.682
Dopamine, n (%)	1 (1.2)	2 (2.5)	0.618
Nitroglycerin, n (%)	12 (14.8)	8 (10.1)	0.370
Visits			
Visits (scheduled and non-scheduled)[a]	5 (4-5)	5 (4-5)	0.175

ACEI = angiotensin converting enzyme inhibitors; ARB = angiotensin II receptor blockers; FED = furosemide equivalent dose; MRA = mineralcorticoid receptor antagonist

[a]Value expressed as median (interquartile range).



Supplementary Figure

Supplementary Table 4 Changes in Serum Potassium

	Usual care	CA125-guided therapy	*P* Value	Omnibus *P* Value
At randomization				
Serum potassium, mEq/L	4.41 ± 0.07	4.52 ± 0.07	0.284	
Clinical categories				0.611
<3.5 mEq/L	3 (3.7)	2 (2.5)		
3.5 to 5.0 mEq/L	67 (82.7)	62 (78.5)		
> 5.0 mEq/L	11 (13.6)	15 (19.0)		
24-h visit				
Serum potassium, mEq/L	4.29 ± 0.07	4.16 ± 0.06	0.195	
Clinical categories				0.270
<3.5 mEq/L	4 (4.9)	9 (11.4)		
3.5 to 5.0 mEq/L	68 (84.0)	64 (81.0)		
> 5.0 mEq/L	9 (11.1)	6 (7.6)		
72-h visit				
Serum potassium, mEq/L	4.12 ± 0.06	4.08 ± 0.06	0.603	
Clinical categories				0.437
<3.5 mEq/L	8 (10.1)	4 (5.1)		
3.5 to 5.0 mEq/L	67 (84.8)	72 (91.1)		
> 5.0 mEq/L	4 (5.1)	3 (3.8)		

CA125 = antigen carbohydrate 125
Continuous variables are expressed as mean ± standard deviation.