Patients with acute heart failure treated with the CARRESS-HF diuretic protocol in association with canrenoate potassium: Tolerance of high doses of canrenoate potassium

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Abbreviated title: Classical diuretics plus canrenoate potassium for AHF

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Summary

Background. – Oral mineralocorticoid receptor antagonists have failed to prove their efficacy for decongestion and potassium homeostasis in acute heart failure. Intravenous mineralocorticoid receptor antagonists have yet to be studied.

Aim. – The aim of this study was to confirm the safety of high-dose potassium canrenoate in association with classic diuretics in acute heart failure.

Methods. – This retrospective single-centre study included consecutive patients who were hospitalized with acute heart failure between 2013 and 2018. One hundred patients with overload treated with the standardized diuretic protocol from the CARESS-HF trial were included. There were no exclusion criteria relating to creatinine or kalaemia at the time of admission. Two groups were constituted on the basis of potassium canrenoate posology: a low-dose group (< 300 mg/day) and a high-dose group (≥ 300 mg/day); the groups were similar in terms of baseline characteristics.

Results. – Mean daily potassium canrenoate doses were 198 mg/day (range 100–280 mg/day) in the low-dose group and 360 mg/day (range 300–600 mg/day) in the high-dose group. There was no significant difference between the high-dose and low-dose groups in terms of mortality, dialysis, renal function, hyperkalaemia, haemorrhage, sepsis or confusion.

Conclusions. – Potassium canrenoate at high doses can be used safely in association with standard diuretics in acute heart failure, even in patients with altered renal function. A prospective study is required to evaluate the efficacy of high-dose potassium canrenoate in preventing hypokalaemia and improving decongestion.

KEYWORDS

Heart failure;

Diuretics;

Renal failure;

Dyskalaemia

Abbreviations: AHF, acute heart failure; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; ICU, intensive care unit; IQR, interquartile range; MRA, mineralocorticoid receptor antagonist; NKCC2, sodium-potassium-chloride cotransporter 2.

Background

Hypokalaemia is a feared complication in hospitalized patients with heart failure (HF) receiving intensive diuretic therapy to treat congestion, which can have an incidence of 40–50% [1, 2]. In these patients, hypokalaemia < 4 mmol/L increases the risk of arrhythmia and sudden death [3][4]. Thus, it has been suggested that the serum potassium concentration should be closely monitored and corrected in patients with HF [5].

High doses of loop diuretics are used in patients with acute heart failure (AHF) to achieve euvolaemia, blocking sodium-potassium-chloride cotransporter 2 (NKCC2) proteins at the apical surface of thick ascending limb cells and inhibiting potassium reabsorption [6, 7]. Moreover, loop diuretics cause important potassium secretion at the distal nephron, where the principal cells take up sodium from the lumen through the epithelial sodium channel in exchange for potassium via sodium-potassium-adenosine triphosphatase [8]. Furthermore, loop diuretics block NKCC2s at the apical membrane of macula densa cells, inhibiting tubuloglomerular feedback. This induced hyperaldosteronism intensifies sodium-potassium exchanges in the distal nephron by stimulating synthesis of the epithelial sodium channel and the renal outer medullary potassium channel.

Potassium supplementation – the most common treatment for hypokalaemia – does not address the causes of hypokalaemia. Therefore, it may be interesting to add potassium-sparing diuretics, such as mineralocorticoid receptor antagonists (MRAs). Adding MRAs may reduce the degree of hypokalaemia and secondary hyperaldosterism induced by loop diuretics [9].

Recently, the ATHENA-HF trial investigated natriuretic doses of spironolactone (i.e. 100 mg) versus standard treatment during management of AHF [10]. There was a trend towards higher serum potassium concentrations in the MRA group, without hyperkalaemia > 5.5 mmol/L. This might be explained by an insufficient MRA dose, leading to a weak antimineralocorticoid effect. Moreover, spironolactone (as with all oral diuretic therapies) has a delayed effect in healthy individuals (48 hours) [11], which is even more pronounced in patients with AHF [12]. The antimineralocorticoid effect of spironolactone may occur too late [10]. Therefore, intravenous MRAs at high doses may be of particular value in preventing a drop in serum potassium concentration during hospitalization for AHF. Potassium canrenoate (Soludactone®; Pfizer Inc., Paris, France) is the only clinically available antimineralocorticoid for parenteral administration worldwide. The maximum recommended daily dosage of potassium canrenoate is 800 mg/day, but in practice it is rarely administered at > 200 mg/day in AHF [13].

The objective of the present study was therefore to describe the safety of high-dose potassium canrenoate in association with standardized diuretic therapy in patients treated for AHF.

Methods

Study design

For this single-centre retrospective cohort study, patients who were hospitalized with AHF in the cardiac intensive care unit (ICU) of Louis Pradel University Hospital (Hospices Civils de Lyon, Lyon, France) between November 2013 and January 2018 were identified. We included consecutive cases of AHF with fluid overload, for which potassium canrenoate was initiated a maximum 24 hours after hospitalization, and loop diuretics administered at admission according to the stepped protocol of the CARESS-HF trial [14]; details of the algorithm are provided in Fig. 1. The study protocol was approved by an ethics committee (Comité d'Ethique du CHU de Lyon).

Diagnosis of fluid overload was made when at least two of the five following conditions were present at admission: peripheral oedema; jugular venous distension; pleural effusion (on chest radiography or echocardiography); ascites; and pulmonary rales/orthopnoea. Central venous pressure was estimated with echocardiography on the basis of inferior vena cava diameter and collapse [15]. There were no exclusion criteria based on left ventricular ejection fraction, or creatinine or potassium concentration at time of admission.

Eligible patients were identified from the electronic case records, with the keywords "acute heart failure", "right heart failure" and "cardiogenic shock" (FileMaker Pro®; Claris, Santa Clara, CA, USA). Data were collected by a single investigator (C. B.) from the patients' electronic medical records: Easily® (Hospices Civils de Lyon, Lyon, France) and ICCA® (Philips Medical, Toronto, ON, Canada). Data were collected for the first 96 hours of hospitalization or up to patient discharge. As 100 mg/day of spironolactone was insufficient to prove its efficacy in the ATHENA-HF trial, and as it has an antimineralocorticoid activity that is 3 times greater than potassium canrenoate equimolar doses [16], a threshold of 300 mg/day was used to stratify the population into a low-dose potassium canrenoate group (< 300 mg/day) and a high-dose group (≥ 300 mg/day).

The primary objective of this study was the safety of high-dose potassium canrenoate in association with the CARESS-HF diuretic protocol in AHF with overload. We evaluated the risk of hyperkalaemia, worsening renal function, dialysis, ventricular arrhythmia, death, haemorrhage and sepsis in the high-dose group compared with the low-dose group. Acute kidney injury was defined in

accordance with the KDIGO recommendations: increase in serum creatinine of 26.5 µmol/L within 48 hours or urine output < 0.5 mL/kg/h for 6 hours or increase in serum creatinine to ≥ 1.5 times baseline [17].

Secondary endpoints were rate of hypokalaemia, change in serum potassium concentration, rate of clinical decongestion at 96 hours or discharge from the cardiac ICU and change in renal function. Clinical decongestion was defined as the absence of peripheral oedema, orthopnoea and jugular venous distension described in the daily notes and discharge summary.

Statistical analysis

Descriptive statistics were performed using StatView software, version 5.0 (SAS Institute, Cary, NC, USA). Quantitative variables are expressed as means (ranges) when the distribution is normal or as medians (interquartile ranges [IQRs]) when this is not the case. Comparisons were made using Student's *t* test or the Wilcoxon signed-rank test, as appropriate. Qualitative variables are expressed as numbers and percentages, and were compared using McNemar's test or the χ^2 test, as appropriate. All tests were two sided, and a *P* value < 0.05 was considered significant.

Results

Baseline patient characteristics

A total of 100 patients were included (Fig. 2). Mean age of the population was 66.6 years (range 30–94 years); 68% of the patients were men, 32% had diabetes mellitus, 46% had hypertension and 39% had ischaemic cardiomyopathy. A total of 40% of the patients had been hospitalized for HF during the previous year. There were 43 patients in the low-dose group and 57 patients in the high-dose group, with no differences in patient characteristics between groups (Table 1 and Table 2). Mean potassium canrenoate dose was 198 mg/day (range 100–280 mg/day) in the low-dose group and 360 mg/day in the high-dose group (range 300–600 mg/day).

The most common signs of overload were peripheral oedema (*n* = 84), rales (*n* = 63) and jugular vein distension (*n* = 62). The estimated right atrial pressure was ≥ 15 mmHg for 79% of the patients, and the estimated systolic pulmonary arterial pressure was ≥ 35 mmHg in 65 of the 68 patients for whom the measure was available.

At admission, 61% of patients had a cardiac index < 2.2 L/kg/min, 23% had a systolic arterial pressure < 90 mmHg, and the median left ventricular ejection fraction (echocardiography) was 35%.

Most patients had altered right ventricular function: 77% had a tricuspid annular S velocity < 9.5 cm/s, and 91% had a tricuspid annular plane systolic excursion (TAPSE) < 17 mm. A total of 57% of patients received dobutamine and 64% received norepinephrine during their first 96 hours in the cardiac ICU.

Diuretic use and fluid balance

Median duration of hospitalization in ICU was 7.0 days (IQR 4.8–9.0 days), the median dosage of loop diuretics over the first 4 days of hospitalization was 1250 mg (IQR 750–2400 mg), and the median number of days on intravenous diuretics over the first 4 days was 4 days (IQR 3–4 days). In addition to receiving loop diuretics, 62% of the participants received treatment with hydrochlorothiazide, and 58% were treated with intravenous inotropic agents.

Median daily urine output was 3.4 L/day (IQR 2.1–4.8 L/day) in the total population, and this decreased over the course of hospitalization. There was no significant difference between the two groups (Table 3 and Fig. 5A). When serial weights were recorded (n = 36), the median weight loss was 6.1 kg (IQR 2.0–9.5 kg) over the duration of diuretic therapy, with no difference between the two groups (Table 4 and Fig. 5B).

Three-quarter (74%) of patients with peripheral oedema at admission no longer did so at 96 hours or discharge (Table 4), and 76% patients achieved clinical euvolaemia at 96 hours or discharge.

Changes in electrolytes

At admission, mean serum potassium concentration was 4.3 mmol/L (range 3.0–6.4mmol/L), 7% of patients had a serum potassium concentration < 3.5 mmol/L and 12% had a serum potassium concentration > 5.0 mmol/L (Table 2 and Fig. 3A). The mean decrease in serum potassium concentration was 0.48 mmol/L (range –1.7 to +3.5 mmol/L) during cardiac ICU stay (Fig. 4A and Fig. 3B and Fig. 5D); the decrease was greatest in the first 24 hours of hospitalization. During hospitalization in the total population, hypokalaemia (defined as serum potassium concentration < 3.5 mmol/L) occurred in 53% of patients, and severe hypokalaemia (defined as serum potassium concentration < 3.0 mmol/L) occurred in 15% of patients. Nearly two-thirds of patients (64%) required potassium supplementation over the course of diuresis; the mean daily dose of oral supplements was 2437 mg (range 600–17,600 mg), and that of intravenous supplements was 4 g (range 1–10.3 g). The mean change in serum potassium concentration was not significantly different between those

receiving high-dose or low-dose potassium canrenoate (Table 5). There was no significant change in calcemia level between admission and discharge in our total population (Fig. 5C).

Adverse events

In our entire study population, five patients had a serum potassium concentration > 5.5 mmol/L and one patient who had a potassium concentration > 6.0 mmol/L during the 96 hours of study treatment. Twelve patients required dialysis, three patients experienced ventricular rhythm abnormalities requiring treatment and six patients died during the 96 hours of hospitalization. There was no significant difference between the high-dose and low-dose groups for all studied adverse events (Table 6). Patients who presented hyperkalaemia (potassium ≥ 5.0 mmol/L) had a higher serum creatinine concentration on admission than those who did not (220 vs 153 µmol/L; $P = 0.009$), and there was no significant difference in the proportion of patients with an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker between those who did or did not undergo dialysis (12.1% vs 13.6%, respectively; $P = 0.99$).

Renal function

In the total population, renal function remained stable over the follow-up, with no significant difference in creatinine concentration between admission and end of follow-up (Fig. 4B and Fig. 5E). Acute kidney injury occurred in 30% of patients. There was an increase in serum creatinine concentration of 26.5 µmol/L within 48 hours for 30 patients, urine output < 0.5 mL/kg/h for 6 hours for three patients and an increase in serum creatinine concentration to ≥ 1.5 times baseline for six patients. Twelve patients were dialyzed after failure of diuretic treatment. After administration of diuretics, renal function improved in 55% of patients; the mean decrease was 46 µmol/L for these patients, without statistical difference between the two groups.

Discussion

The present study found that high-dose potassium canrenoate can be used safely. There were very few cases of hyperkalaemia, and the other adverse events were expected in such a population, without statistical difference between the high-dose and low-dose groups. More specifically, there was no case of hyperkalaemia with potassium canrenoate, even among patients with kalaemia > 5.0 mM at admission or with severe impaired renal function, despite theoretical contraindication. HF guidelines

recommend avoiding MRAs only in patients with an estimated glomerular filtration rate < 30 mL/min or serum potassium concentration > 5.0 mmol/L [18-21]. However, even in this fragile population, the results of the present observational study suggest that MRA treatment could be possible, with close clinical and laboratory monitoring of hospitalized patients and the short-term use of intravenous MRAs. This is an important message, as MRAs are underused because of a fear of hyperkalaemia, despite having shown a clear benefit in chronic HF [22-24]. The study population was well treated, with MRA prescriptions for 56% of patients with HF with reduced ejection fraction (HFrEF) before admission (seven cases of missing data for admission treatment for the 41 patients with HFrEF). By comparison, among the eligible patients with HFrEF in the CHAMP-HF registry in 2018 in the USA, 33.4% were treated with MRAs. It should be remembered that European HF guidelines in 2016 recommended (Class 1a) introducing an MRA for patients with HFrEF (ejection fraction < 40%) who remain symptomatic despite treatment with an angiotensin-converting enzyme inhibitor and a beta-blocker, to reduce the risk of HF hospitalization and death.

This study is also interesting in terms of establishing data about the prevalence of hypokalaemia in acute decompensated HF treated with intravenous diuretics; such data are very difficult to find. Overall, 53% of our population experienced hypokalaemia < 3.5 mmol/L, which is consistent with the rest of the literature.

This is the first study of intravenous MRA treatment in patients with AHF. However, the safety data we have reported are in accordance with the results of a study in cirrhosis-related ascites conducted in the late 1980s, which found potassium canrenoate 600 mg/day to be safe, without appearance of hyperkalaemia [25]. Furthermore, the ATHENA-HF trial, which investigated oral MRA treatment in AHF, found that high-dose spironolactone was well tolerated; there was no significant difference in terms of renal function, hyperkalaemia or other serious events between arms [10].

Study limitations

This study does, however, have several limitations as a consequence of the retrospective design. Selection bias could have affected the comparison between the low-dose and high-dose groups, as the dose of potassium canrenoate was not standardized, but left to the discretion of the physician. Nevertheless, there was no significant difference between the two groups in terms of baseline characteristics. It is also of note that relatively few patients were included over the study period compared with the number of admissions to the ICU for AHF – a consequence of strict inclusion

criteria concerning the definition of overload and administration of diuretics. This enabled us to have standardized loop diuretic administration using the CARESS-HF protocol. Some deviations to the CARESS-HF protocol were described, with a 26% rate of inappropriate administration of thiazide; the bolus administration of furosemide was not studied. Moreover, urinary ionograms were not available, but it would be interesting to be able to detect a potential MRA responder in AHF with the 24-hour urinary sodium:potassium ratio [26, 27]. A study has shown that a sodium:potassium ratio < 1 under loop diuretics, signifying increased endogenous mineralocorticoid secretion, was associated with increased diuresis when an MRA was added [28]. Finally, there was no control group without potassium canrenoate, which precludes any conclusion as to the effectiveness of this treatment.

Conclusions

High-dose potassium canrenoate can be used safely in combination with loop diuretics in AHF, with close surveillance and serial laboratory measures. A prospective study for efficacy is needed to compare loop diuretic monotherapy, standardized as in the CARESS-HF trial, versus intravenous MRA combined with standardized loop diuretics in AHF with clinical overload.

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None.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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Figure legends

Figure 1. Stepped combined diuretic protocol for the CARESS-HF trial. BD: twice a day; EF: ejection fraction; iv: intravenous; LVAD: left ventricular assist device; QD: once a day; RV: right ventricular; SBP: systolic blood pressure; UF: urine flow; UO: urine output.

Figure 2. Flow chart. Eligible patients were found with the keywords “acute heart failure”, “right heart failure” and “cardiogenic shock”. AHF: acute heart failure; ICU: intensive care unit.

Figure 3. A. Distribution of kalaemia at admission in the total population. B. Distribution of in-hospital kalaemia change between admission and end of follow-up in the total population.

Figure 4. Evolution of kalaemia and renal function during follow-up. A. Kalaemia from admission to end of follow-up. B. Creatininaemia from admission to end of follow-up.

Figure 5. A. Change in urine output between admission and Day 4. B. Change in weight between admission and Day 4. C. Change in calcaemia between admission and Day 4. D. Change in kalaemia between admission and Day 4. E. Change in estimated glomerular filtration rate (eGFR) between admission and Day 4. [production: please swap A and B in the final figure, so urine volume first and weight second]

Table 1 Patient characteristics.

	Total population	Posology of potassium canrenoate		*P*
		< 300 mg/day	≥ 300 mg/day	
	(*n* = 100)	(*n* = 43)	(*n* = 57)	
Demographics				
Mean age (years)	66.6 (30–94)	68.5 (41–90)	65.2 (30–94)	0.21
Male sex	68 (68)	65 (65)	70 (70)	0.59
Median BMI (kg/m^2)	27 (23.5–32)	27 (24–33)	27 (23–31)	0.59
Co-morbidities				
Diabetes mellitus	32 (32)	15 (35)	12(30)	0.59
Hypertension	46 (46)	23 (53)	23 (40)	0.19
Current smoker	18 (18)	6 (14)	12 (22)	0.42
Dyslipidaemia	30 (30)	12 (28)	18 (32)	0.69
Chronic kidney disease	25 (26)	9 (21)	16 (29)	0.42
Usual treatment before hospitalization				
ACE inhibitor or ARB	59 (64)	24 (63)	35 (65)	0.86
Beta-blocker	50 (54)	22 (57)	28 (52)	0.57
Aldosterone antagonist	34 (38)	16 (45)	18 (34)	0.32
Median furosemide dose (mg/day)	120 (40–205)	122 (40–160)	100 (40–213)	0.25
Thiazide diuretics	5 (6)	0 (0)	5 (10)	0.92
Loop diuretic	73 (83)	28 (77)	45 (87)	0.26
CRT	18 (20)	12 (31)	6 (11)	0.09
Implanted defibrillator	24 (26)	14 (35)	10 (19)	0.06
Previous cardiac history				
Ischaemic cardiopathy	39 (39)	21 (49)	18 (32)	0.08
Mean LVEF (%)	42 (15–60)	41 (15–60)	42 (15–60)	0.93
HFrEF	41 (43)	19 (49)	19 (33)	
HFmrEF	13 (14)	5 (13)	8 (14)	
HFpEF	42 (44)	15 (38)	27 (47)	

Data are expressed as mean (range), number (%) or median (interquartile range). ACE: angiotensin-

converting enzyme; ARB: angiotensin II receptor blocker; BMI: body mass index; CRT: cardiac resynchronization therapy; HFmrEF: heart failure with mid-range ejection fraction; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; LVEF: left ventricular ejection fraction.

Table 2 Clinical, echocardiographic and laboratory characteristics at admission.

	Total population	Posology of potassium canrenoate		*P*
		< 300 mg/day	≥ 300 mg/day	
	(*n* = 100)	(*n* = 43)	(*n* = 57)	
Clinical characteristics				
Median systolic blood pressure (mmHg)	107 (90–125)	110 (90–125)	104 (90–120)	0.48
Median heart rate (beats/min)	87 (75–102)	84 (70–94)	89 (78–112)	0.12
Jugular venous distension	62 (62)	30 (70)	32 (56)	0.16
Rales	63 (63)	24 (56)	39 (68)	0.20
Peripheral oedema	84 (84)	36 (83)	48 (84)	0.95
Orthopnoea	32 (32)	11 (25)	21 (38)	0.44
NYHA class III or IV	50 (57)	20 (55)	30 (58)	0.75
Ascites	13 (13)	7 (16)	6 (11)	0.42
Pleural effusion	38 (40)	16 (39)	22 (41)	0.87
Echocardiographic characteristics				
Mean cardiac output (L/min)	4.0 (1.7–9.2)	3.9 (1.8–9.2)	4.1 (1.7–7.5)	0.55
Median sPAP (mmHg)	60 (51–71)	60 (49–70)	60 (52–73)	0.86
Median right atrial pressure (mmHg)	20 (15–20)	20 (15–20)	20 (15–20)	0.71

Right ventricular systolic function				
Median TAPSE (mm)	12 (9–15)	12 (9.5–15)	12 (9.5–15)	0.65
Median DTI S' wave (cm/s)	8 (6–9)	8 (6–9)	8 (6–9)	0.49
Median LVEF (%)	35 (20–50)	37 (25–50)	30 (20–50)	0.11
Mean systemic vascular resistance (dynes/s/cm^{-5})	1200 (900–1600)	1350 (400–2500)	1260 (500–3000)	0.32
Laboratory values at admission				
Median sodium (mEq/L)	136 (131–139)	136 (132–139)	135 (131–139)	0.73
Mean potassium (mEq/L)	4.3 (3.0–6.4)	4.3 (3.1–5.8)	4.3 (3.0–6.4)	0.93
Median blood urea nitrogen (mg/dL)	15 (9–24)	15 (9–24)	14 (9–24)	0.89
Median creatinine (µmol/L)	148 (101–212)	146 (98–190)	150 (107–217)	0.63
Median BNP[a] (ng/L) (*n* = 63)	1599 (788–3018)	1638 (790–2463)	1499 (805–3162)	0.55
Median bicarbonate (mEq/L)	23 (20–26)	23 (21–26)	23 (20–25)	0.13
Mean calcaemia (mEq/L)	2.23 (1.56–2.56)	2.21 (1.56–2.47)	2.24 (1.95–2.56)	0.40
Mean protidaemia (g/L)	66 (18–88)	66 (52–78)	65 (51–88)	0.48
Median haemoglobin (g/L)	120 (102–135)	120 (104–132)	120 (99–137)	0.99
Median SvO_2 (%) (*n* = 23)	51 (41–66)	60 (48–64)	49 (40–70)	0.84
Median haematocrit (%)	38 (32–42)	38 (34–41)	38 (31–42)	0.84

Data are expressed as median (interquartile range), number (%) or mean (range). BNP: brain natriuretic peptide; DTI: Doppler tissue imaging; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; sPAP: systolic pulmonary artery pressure SvO_2: mixed venous oxygen saturation; TAPSE: tricuspid annular

plane systolic excursion.

[a] ARCHITECT chemiluminescent microparticle immunoassay (CMIA); Abbott Laboratories, Chicago, IL, USA.

Table 3 Net urine output.

	Total population	Posology of potassium canrenoate		*P*
		< 300 mg/day	≥ 300 mg/day	
24 hours	4010 (2490–6335)	3927 (1330–6610)	3927(2720–6120)	0.44
48 hours	3500 (2375–4925)	3540 (1870–4800)	3000 (3000–4900)	0.07
72 hours	3200 (2100–4250)	2850 (1875–4025)	3300 (2200–5000)	0.12
96 hours	2650 (1800–4175)	2600 (1775–3900)	2550 (1800–4350)	0.51

Data are expressed as median (interquartile range) mL/day.

Table 4 Change between admission and end of follow-up (96 hours or earlier discharge).

	Admission	End of follow-up	*P*[a]
Clinical characteristics			
Peripheral oedema	84	22	< 0.0001
Weight change (kg)	77.0 (63–90)	74.4 (61–86)	< 0.0001
Systolic blood pressure (mmHg)	107 (90–125)	98 (88–110)	0.002[b]
Diastolic blood pressure (mmHg)	65 (56–80)	60 (53–65)	< 0.0001
Heart rate (beats/min)	87 (75–102)	87 (74–99)	0.88
Laboratory values			
Blood urea nitrogen (mg/dL)	14 (7–25)	17 (9–26)	0.07
Creatinine (µmol/L)	144 (94–217)	137 (103–195)	0.65
Protidaemia (g/L)	63 (60–68)	65 (61–69)	0.16
Haematocrit (%)	36 (32–41)	37 (32–42)	0.02
Sodium (mmol/L)	136 (132–140)	135 (131–139)	0.93
Potassium (mmol/L)	4.3 (3.8–4.7)	3.8 (3.4–4.2)	< 0.0001[b]
Calcaemia (mmol/L)	2.23 (2.12–2.32)	2.27 (2.16–2.37)	0.06

Data are expressed as % or median (interquartile range).

[a] Wilcoxon test.

[b] Student's *t* test for paired variables.

Table 5 Change in kalaemia between admission and 96 hours or earlier discharge, according to dose of potassium canrenoate.

	Posology of potassium canrenoate		*P*[a]
	< 300 mg/day (n = 42)[b]	≥ 300 mg/day (n = 57)	
Change in kalaemia (mmol/L)	–0.47 (–2.70 to +1.70)	–0.49 (–3.10 to +1.50)	0.95

Data are expressed as mean (range).

[a] Student's *t* test.

[b] One missing value.

Table 6 Serious adverse events.

	Total population	Posology of canrenoate potassium		*P*
		< 300 mg/day	≥ 300 mg/day	
	(*n* = 100)	(*n* = 43)	(*n* = 57)	
Dialysis	12 (12)	5 (12)	7 (12)	0.92[a]
Acute kidney injury	30 (30)	12 (28)	18 (32)	0.86[a]
Confusion	9 (9)	4 (9)	5 (9)	0.99[b]
Sepsis	35 (35)	13 (30)	22 (39)	0.51[a]
Ventricular arrythmia	3 (3)	2 (5)	1 (2)	
All-cause death	6 (6)	2 (5)	4 (7)	
Haemorrhage	1 (1)	0 (0)	1 (2)	
Kalaemia > 5.0 mmol/L	18 (18)	10 (23)	8 (14)	0.35[a]
Kalaemia > 5.5 mmol/L	5 (5)	2 (5)	3 (5)	
Kalaemia > 6.0 mmol/L	1 (1)	0 (0)	1(2)	

Data are expressed as number (%).

[a] χ^2 test.

[b] Fisher's exact test.

At randomization-stepped pharmacological care arm

UO > 5 L/day ► Reduce current diuretic regimen *if desired*
UO > 3-5 L/day ► Continue current diuretic regimen
UO < 3 L/day ► See table

	Current dose		Suggested dose	
	Loop (/day)	Thiazide	Loop (/day)	Thiazide
A	≤ 80	+ or -	40 mg iv bolus + 5 mg/ hr	0
B	81-160	+ or -	80 mg iv bolus + 10 mg/ hr	5 mg metazolone QD
C	161-240	+ or -	80 mg iv bolus + 20 mg/ hr	5 mg metazolone BID
D	> 240	+ or -	80 mg iv bolus + 30 mg/ hr	5 mg metazolone BID

At 24 hours-stepped pharmacological care arm

Persistent volume overload present
UO > 5 L/day ► Reduce current diuretic regimen *if desired*
UO > 3-5 L/day ► Continue current diuretic regimen
UO < 3 L/day ► Advance to next step on table

At 48 hours-stepped pharmacological care arm

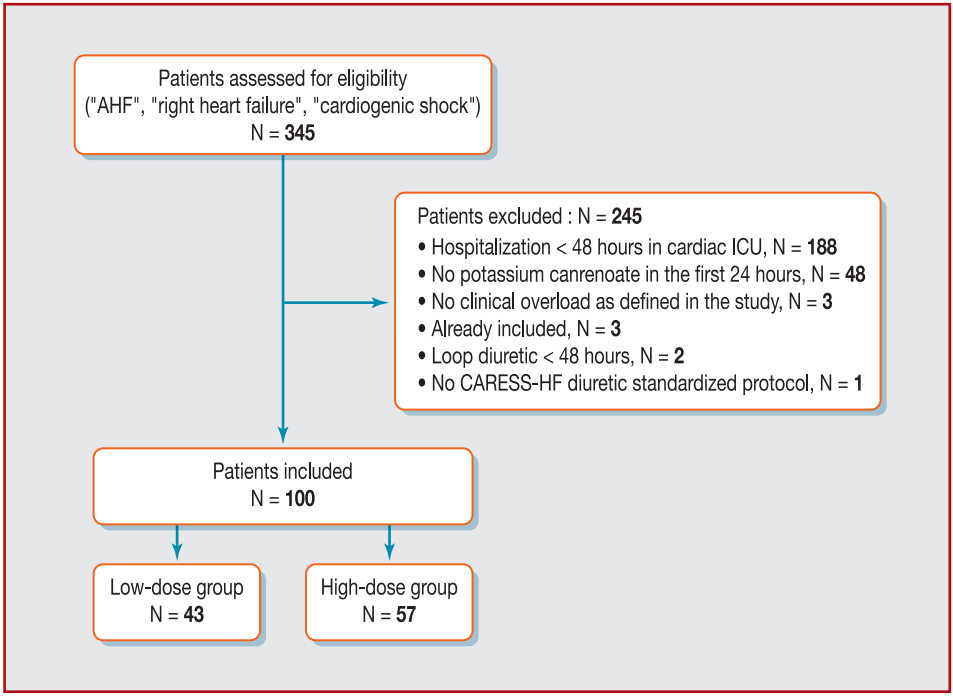
Persistent volume overload present
UO > 5 L/day ► Reduce current diuretic regimen *if desired*
UO > 3-5 L/day ► Continue current diuretic regimen
UO < 3 L/day ► Advance to next step on table and consider :
Dopamine or dobutamine at 2 ug/kg/hr if SBP < 110 mmHg and EF < 40% or RV systolic dysfunction.
Nitroglycerin or nesiritide if SBP > 120 mmHg (any EF) and severe symptoms.

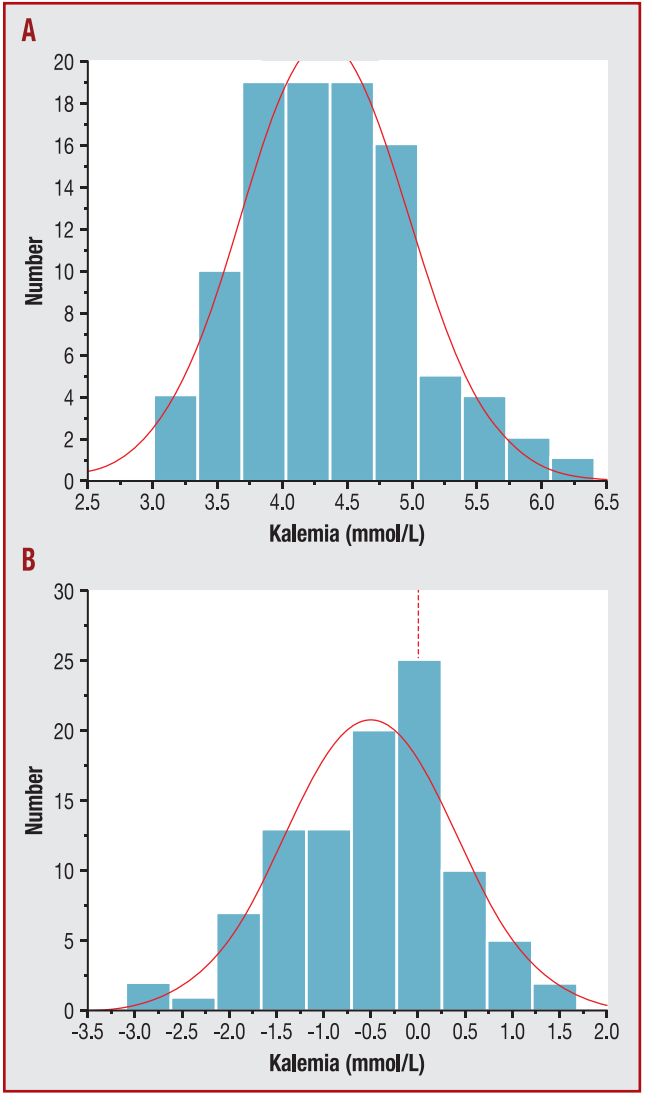
At 72 hours-stepped pharmacological care arm

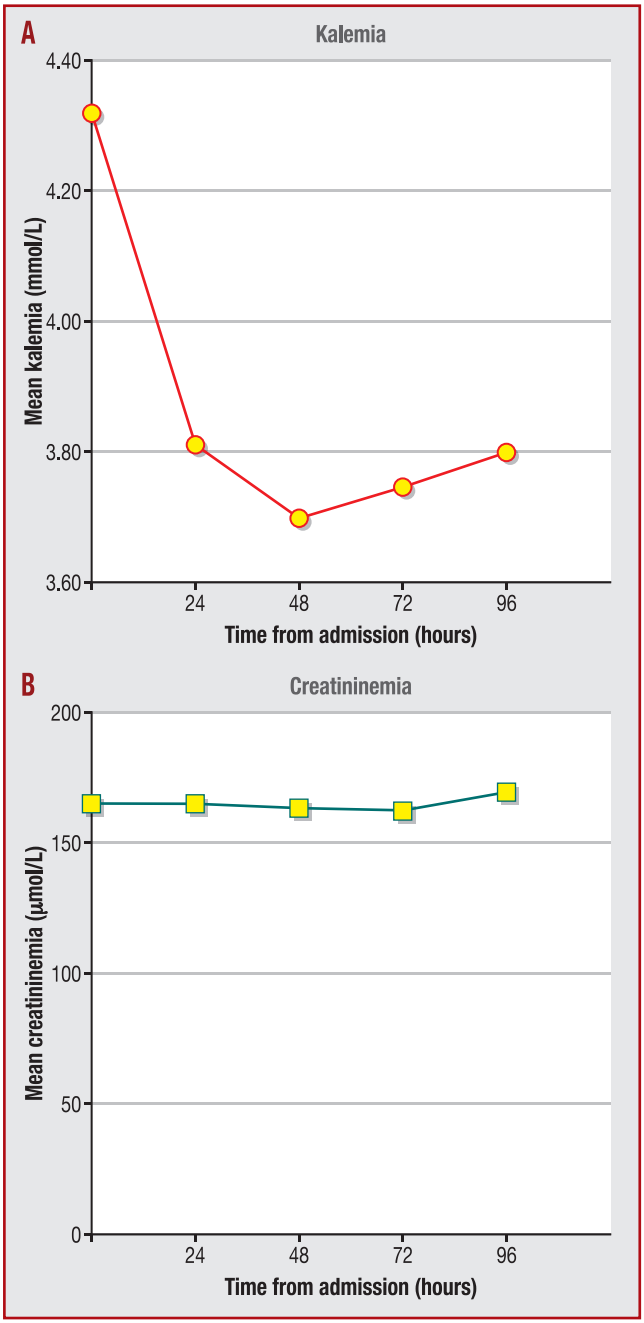
Persistent volume overload present
UO > 5 L/day ► Reduce current diuretic regimen *if desired*
UO > 3-5 L/day ► Continue current diuretic regimen
UO < 3 L/day ► Advance to next step on table and consider :
Dopamine or dobutamine at 2 ug/kg/hr if SBP < 110 mmHg and EF < 40% or RV systolic dysfunction.
Nitroglycerin or nesiritide if SBP > 120 mmHg (any EF) and severe symptoms.
Advanced cardiorenal therapy, hemodynamic-guided iv therapy, LVAD, dialysis or UF cross-over.

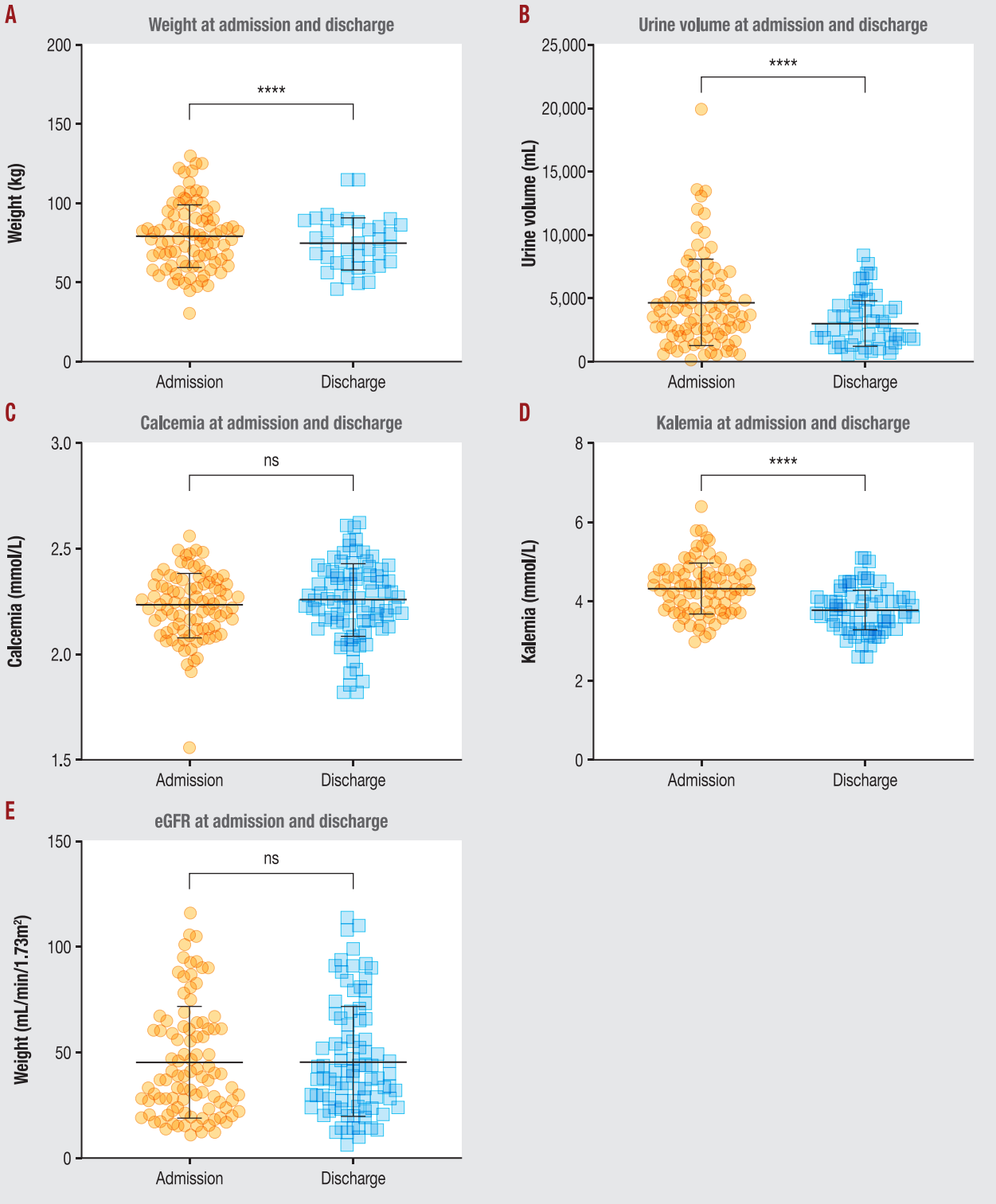
At 96 hours-stepped pharmacological care arm

Persistent volume overload present
UO > 5 L/day ► Reduce current diuretic regimen *if desired*
UO > 3-5 L/day ► Continue current diuretic regimen
UO < 3 L/day ► Advance to next step on table and consider :
Dopamine or dobutamine at 2 ug/kg/hr if SBP < 110 mmHg and EF < 40% or RV systolic dysfunction.
Nitroglycerin or nesiritide if SBP > 120 mmHg (any EF) and severe symptoms.
Advanced cardiorenal therapy, hemodynamic-guided iv therapy, LVAD, dialysis or UF cross-over.


Patients assessed for eligibility
("AHF", "right heart failure", "cardiogenic shock")
N = 345
Patients excluded : N = 245
• Hospitalization < 48 hours in cardiac ICU, N = 188
• No potassium canrenoate in the first 24 hours, N = 48
• No clinical overload as defined in the study, N = 3
• Already included, N = 3
• Loop diuretic < 48 hours, N = 2
• No CARESS-HF diuretic standardized protocol, N = 1
Patients included
N = 100
Low-dose group
N = 43
High-dose group
N = 57


A
Number
Kalemia (mmol/L)
B
Number
Kalemia (mmol/L)


A
Kalemia
4.40
4.20
4.00
3.80
3.60
Mean kalemia (mmol/L)
24
48
72
96
Time from admission (hours)
B
Creatininemia
200
150
100
50
0
Mean creatininemia (µmol/L)
24
48
72
96
Time from admission (hours)


A
Weight at admission and discharge
Weight (kg)
200
150
100
50
0
****
Admission
Discharge
B
Urine volume at admission and discharge
Urine volume (mL)
25,000
20,000
15,000
10,000
5,000
0
****
Admission
Discharge
C
Calcemia at admission and discharge
Calcemia (mmol/L)
3.0
2.5
2.0
1.5
ns
Admission
Discharge
D
Kalemia at admission and discharge
Kalemia (mmol/L)
8
6
4
2
0
****
Admission
Discharge
E
eGFR at admission and discharge
Weight (mL/min/1.73m²)
150
100
50
0
ns
Admission
Discharge