

Role of Early Assesment of Diuresis and Natriuresis in Detecting In-Hospital Diuretic Resistance in Acute Heart Failure

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García-Magallón B, Cobo-Marcos M, Martiarena AD, Hernández EM, Martín Jiménez ML, García AM, De Castro Campos D, Martín PV, Terciado FH, González RG, Matutano Muñoz A, Escribano García D, Domínguez F, Sainz Herrero A, Gómez Peñalba C, Garcia-Pavia P and Segovia J (2022) Role of Early Assesment of Diuresis and Natriuresis in Detecting In-Hospital Diuretic Resistance in Acute Heart Failure. Front. Physiol. 13:887734. doi: 10.3389/fphys.2022.887734 ¹Department of Cardiology, Hospital Universitario Puerta de Hierro Majadahonda, IDIPHISA, Madrid, Spain, ²Centro de Investigación Biomédica en Red en Enfermedades Cardiovasculares (CIBERCV), Madrid, Spain, ³Emergency Department, Hospital Universitario Puerta de Hierro Majadahonda, IDIPHISA, Madrid, Spain, ⁴Department of Internal Medicine, Hospital Universitario Puerta de Hierro Majadahonda, IDIPHISA, Madrid, Spain, ⁵Department of Laboratory of Biochemistry-Clinical Analysis, Hospital Universitario Puerta de Hierro Majadahonda, IDIPHISA, Madrid, Spain, ⁶Universidad Francisco de Vitoria (UFV), Madrid, Spain

Background and Purpose: European Guidelines recommend early evaluation of diuresis and natriuresis after the first administration of diuretic to identify patients with insufficient diuretic response during acute heart failure. The aim of this work is to evaluate the prevalence and characteristics of patients with insufficient diuretic response according to this new algorithm.

Methods: Prospective observational single centre study of consecutive patients with acute heart failure and congestive signs. Clinical evaluation, echocardiography and blood tests were performed. Diuretic naïve patients received 40 mg of intravenous furosemide. Patients on an oupatient diuretic regimen received 2 times the ambulatory dose. The diuresis volume was assessed 6 h after the first loop diuretic administration, and a spot urinary sample was taken after 2 h. Insufficient diuretic response was defined as natriuresis <70 mEq/L or diuresis volume <600 ml.

Results: From January 2020 to December 2021, 73 patients were included (59% males, median age 76 years). Of these, 21 patients (28.8%, 95%Cl 18.4; 39.2) had an insufficient diuretic response. Diuresis volume was <600 ml in 13 patients (18.1%), and 12 patients (16.4%) had urinary sodium <70 mEq/L. These patients had lower systolic blood pressure, worse glomerular filtration rate, and higher aldosterone levels. Ambulatory furosemide dose was also higher. These patients required more frequently thiazides and inotropes during admission.

Conclusion: The diagnostic algorithm based on diuresis and natriuresis was able to detect up to 29% of patients with insufficient diuretic response, who showed some characteristics of more advanced disease.

Keywords: diuretic, acute heart failure, natriuresis, diuretic response, diuretic resistance

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INTRODUCTION

Signs and symptoms of congestion are usually the most common manifestations among patients with acute heart failure (HF) (Adams et al., 2005), and intravenous loop diuretics remain the most widely used therapy to achieve euvolaemia (Fonarow et al., 2004). Diuretic response is defined as the capacity of diuretics to induce natriuresis and diuresis (ter Maaten et al., 2015a).

Identification of patients who may have a poor diuretic response is one of the most important challenges in the field of HF, since a poor diuretic response is associated with a higher risk of rehospitalization and increased mortality (Metra et al., 2012; Neuberg et al., 2002; Valente et al., 2014; ter Maaten et al., 2015b; Testani et al., 2014; Voors et al., 2014). To date, no uniform and standard definition was available to allow the early identification of patients at risk of developing resistance to diuretic treatment during HF hospitalization.

The Position Statement from the Heart Failure Association of the European Society of Cardiology about the use of diuretics in heart failure with congestion (Mullens et al., 2019), and more recently the European Guidelines for the diagnosis and treatment of acute and chronic heart failure (McDonagh et al., 2021), have proposed an algorithm that includes the early assessment of diuresis and natriuresis after the first administration of loop diuretics in patients with acute HF, in order to detect patients with insufficient diuretic response who might benefit from diuretic intensification.

To date, data on the prevalence of early diuretic resistance according to these parameters have not yet been described.

The aim of this work is to evaluate the prevalence and features of acute HF patients who present an insufficient diuretic response according to this algorithm.

METHODS

From January 2020 to December 2021, we conducted a prospective, observational and single centre study on a sample of consecutive patients aged \geq 18 years whose primary admission diagnosis was acute HF and were admitted to the cardiology department. The diagnosis of acute HF was based on the current ESCF HF guidelines. In addition, NTproBNP >300 pg/dl and the presence of at least two of the following congestion criteria were required: jugular venous pressure >10 cm, lower limb edema, ascites, or pleural effusion determined by chest x-ray or pulmonary ultrasound.

Patients in cardiogenic shock and/or on dialysis were excluded. Patients in whom urine output or natriuresis could not be recorded or were missed were also excluded.

Study Procedures and Statistical Analysis

Complete clinical evaluation, echocardiogram and laboratory tests were performed. Diuretic naïve patients received 40 mg of intravenous furosemide. Patients on an outpatient diuretic regimen received 2 times the home dose. The diuresis volume was assessed 6 h after the first loop diuretic administration, and a spot urinary sample was taken after 2 h. Urinary sodium was measured using a Siemens

Dimension EXL chemistry analyzer. Insufficient diuretic response was defined as natriuresis <70 mEq/L or diuresis volume <600 ml.

Values of continuous variables are given as the median and interquartile range (IQR). Categorical variables are described in absolute and relative frequencies. The associations between clinical characteristics and diuretic response were analyzed by univariate analysis using the Chi square test for categorical variables and the Mann-Whitney U test for continuous variables. A *p*-value <0.05 was considered significant. All analyses were performed using STATA v.13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX) and R software (R Foundation for Statistical Computing, version 3.6.0).

The present study conforms to the principles of the Declaration of Helsinki. Approval from the local ethics committee/internal review board was obtained at the participating centers and patients signed an informed consent.

RESULTS

From January 2020 to December 2021, 694 patients were admitted for acute HF. Nearly 50% of these patients did not meet the inclusion criteria as they presented predominant pulmonary congestion. About 30% could not be included as the treating physician didn't follow the ESC protocol, in part due to Covid-19 pandemic.

A final sample of 73 patients were included (59% males, median age 76 years [IQR: 70–85]). Four initially included patients were not finally analysed as urinary output was not correctly collected. Of the remaining sample (73/78), 21 patients (28.8%) met the definition of early insufficient diuretic response.

The diuresis volume was <600 ml in 13 patients (18.1%), and 12 patients (16.4%) had urinary sodium <70 mEq/L. Only 4 patients (5.5%) had both low urinary sodium and decreased urine output.

Compared with patients with an adequate diuretic response, these patients had lower systolic blood pressure (133 mmHg [IQR: 116–148] vs. 148 [IQR: 124–175], p = 0.043), worse glomerular filtration rate (49 ml/min/1.73 m² [IQR: 28–63] vs. 69 [44–86], p = 0.044), and showed greater neurohormonal activation (aldosterone levels: 19 ng/dl [IQR: 11–40] vs. 10 [IQR: 7–14], p = 0.005). This group of patients presented a higher percentage of previous admission due to HF (42.9 vs. 17.6%, p = 0.025), and their basal furosemide dose was also higher (80 mg [IQR: 5–88] vs. 40 [IQR: 0–60], p = 0.032) **Table 1**.

During admission, patients with poor diuretic response required more frequently inotropes (19 vs. 0%, p = 0.001), and thiazides (52.4 vs. 23.1%, p = 0.015).

DISCUSSION

To date, this is the first study to show the performance of the algorithm proposed by the HF European guidelines for the early assessment of diuretic response in a cohort of patients with acute HF.

This algorithm based on diuresis volume and natriuresis was able to detect up to 29% of patients with insufficient diuretic response who might benefit from enhanced diuretic treatment.

TABLE 1 | Legend. Patient characteristics per diuretic response (n = 73).

$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Patient characteristics per diuretic response	All patients $n = 73$	Poor DR <i>n</i> = 21 (28.8%)	Good DR <i>n</i> = 52 (71.2%)	<i>p</i> -value
App (pager)* Ap (C+65) Ap (C+65) Ap (C+65) BBAB Debotes millus 2, n (%) 29 (39.7) 12 (57.1) 31 (39.8) D.846 Debotes millus 2, n (%) 29 (39.7) 12 (57.1) 17 (32.7) D.137 Aprine Inperfersion, n (%) 62 (24.6) 11 (80.7) 29 (65.6) D.444 Ap (25.6) 14 (40.7) 29 (65.6) 5 (22.8) 21 (40.4) D.260 Ap (25.6) 5 (22.8) 21 (40.4) D.260 Heart lature evolution (daps)* 232 (0-100.7) D.262 Basel Institute evolution (daps)* 230 (0-100.7) 430 (0-20.0) 232 (0-101.7) D.260 Basel Institute evolution (daps)* 240 (0-20.0) 6 (17.7) D.3 (60.0) D.33 Ambutatory functionands dose* (mg) 40 (66) 15 (71) D.3 (60.0) D.043 Ambutatory functionands dose* (mg) 40 (66) 16 (71) D.3 (60.0080 D.345 Ambutatory functionands dose* (mg) 41 (65.7) D.4 (40.000.0080 D.441 D.4 (40.000.0080 D.441 Ambutatory functionands 2 (1-3)					
$\begin{split} \text{Mate } n(\mathbf{e}) & \text{ds} \ (\mathbf{e}) & \text{ds} \ (\mathbf{e}, \mathbf{e}) & \text{ds} \ (\mathbf{e}, \mathbf{e}, \mathbf{e}) & \text{ds} \ (\mathbf{e}, \mathbf{e}) & \text{ds} \ (\mathbf{e}, $	Age (years) ^a	76 (70–85)	76 (50–87)	78 (70–85)	0.845
Debetes melta 2, r (%) 29 (947) 12 (57.) 17 (22.1) 0.137 Chrone kathry desease, r (%) 77 (23.3) 6 (22.6) 11 (21.1) 0.575 Chrone kathry desease, r (%) 77 (23.3) 6 (22.6) 11 (21.1) 0.575 Chrone kathry desease, r (%) 74 (86.9) 14 (86.7) 29 (56.9) 0.441 Perioda hospitalization for hear tailure, r (%) 18 (24.7) 9 (42.9) 9 (17.6) 0.025 Encono HF, r (%) 74 (40.4) 0.280 Hear tailure exclution (days) ^a 293 (01963) 436 (0-3.030) 232 (0-1.647) 0.280 Basel treatment Funcembe dese ^a (mg) 40 (0-50) 50 (5-58) 40 (0-670) 0.032 MFA, r (%) 8 (11) 2 (10) 6 (12) 0.032 MFA, r (%) 8 (11) 2 (10) 6 (12) 0.032 MFA, r (%) 8 (11) 2 (10) 6 (12) 0.032 MFA, r (%) 8 (11) 2 (10) 6 (12) 0.032 MFA, r (%) 8 (11) 2 (10) 6 (12) 0.032 MFA, r (%) 8 (11) 2 (10) 6 (12) 0.032 MFA, r (%) 8 (11) 2 (10) 6 (12) 0.032 MFA, r (%) 8 (11) 1 (6) 2 (4) 0.00 MFA, r (%) 3 (4) 1 (6) 2 (4) 0.00 MFA, r (%) 3 (4) 1 (6) 2 (4) 0.00 MFA, r (%) 3 (4) 1 (6) 2 (4) 0.00 MFA, r (%) 3 (4) 1 (6) 2 (4) 0.00 MFA, r (%) 3 (4) 1 (6) 2 (4) 0.00 MFA, r (%) 3 (4) 1 (6) 2 (4) 0.00 MFA, r (%) 3 (4) 1 (6) 2 (4) 0.00 MFA, r (%) 3 (4) 1 (6) 2 (4) 0.00 MFA, r (%) 3 (4) 1 (6) 2 (4) 0.00 MFA, r (%) 3 (4) 1 (6) 2 (4) 0.00 MFA, r (%) 3 (4) 1 (6) 2 (4) 0.00 MFA, r (%) 3 (4) 1 (6) 2 (4) 0.00 MFA, r (%) 3 (4) 1 (6) 2 (4) 0.00 MFA, r (%) 3 (4) 1 (6) 2 (4) 0.00 MFA, r (%) 3 (4) 1 (6) 2 (4) 0.00 MFA, r (%) 3 (4) 1 (62) 1 (7, 10, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0	Male n (%)	43 (58.9)	12 (57.1)	31 (59.6)	0.846
$\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$	Diabetes mellitus 2, n (%)	29 (39.7)	12 (57.1)	17 (32.7)	0.137
$\begin{split} & \text{Chronic Midney disease, $n^{(b)}_{(b)}$ 17 (22.3) 6 (28.6) 11 (21.1) 0.575 \\ & \text{Markin Emission, $n^{(b)}_{(b)}$ 18 (24.7) 9 (42.9) 9 (17.6) 0.225 \\ & \text{Markin Emission, $n^{(b)}_{(b)}$ 18 (24.7) 9 (42.9) 9 (17.6) 0.225 \\ & \text{Heart failure evolution (disys)a 233 (0-1965) 436 (0-3.030) 232 (0-1.547) 0.250 \\ & \text{Heart failure evolution (disys)a}_{(c)}$ 233 (0-1965) 436 (0-3.030) 232 (0-1.547) 0.250 \\ & \text{Basel treatment } \\ & \text{Fursemide, $n^{(b)}_{(b)}$ 49 (66) 15 (71) 33 (64) 0.594 \\ & \text{Anculatory theoremide docea (mg) 40 (0-60) 80 (5-82) 40 (0-60) 0.032 \\ & \text{MRA, $n^{(b)}_{(c)}$ 11 (2 (10) 6 (17) 0.33 (64) 0.039 \\ & \text{MRA, $n^{(b)}_{(c)}$ 11 (2 (10) 6 (17) 0.33 (64) 0.039 \\ & \text{MRA, $n^{(b)}_{(c)}$ 11 (2 (10) 6 (17) 0.33 (64) 0.039 \\ & \text{MRA, $n^{(b)}_{(c)}$ 11 (2 (10) 6 (17) 0.33 (64) 0.039 \\ & \text{Accelatory theoremide docea (mg) 40 (0-60) 80 (5-82) 40 (0-630 0.039 \\ & \text{MRA, $n^{(b)}_{(c)}$ 11 (2 (10) 6 (17) 0.33 (64) 0.039 \\ & \text{MRA, $n^{(b)}_{(c)}$ 11 (2 (10) 6 (17) 0.33 (64) 0.039 \\ & \text{Accelatory theoremide docea (mg) 44 (0,0-00 0.039 0.039 \\ & \text{MRA, $n^{(b)}_{(c)}$ 13 (44) 15 (2 (2 (4) 0.030 0.042 7) 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0$	Arterial hypertension, n (%)	62 (84.9)	18 (85.7)	44 (84.6)	0.905
$\begin{aligned} & \text{Arial Hindlation, r, P(b) & 43 (68.9) & 14 (66.7) & 29 (65.9) & 0.441 \\ & \text{Previous hospitatication for heat failure, r, P(b) & 26 (55.6) & 5 (23.8) & 21 (40.4) & 0.280 \\ & \text{Heat failure exclution (days)^* & 290 (0-1965) & 436 (0-3.030) & 232 (0-1.647) & 0.259 \\ & \text{Basel treatment} & & & & & & & & & & & & & & & & & & &$	Chronic kidney disease, n (%)	17 (23.3)	6 (28.6)	11 (21.1)	0.575
Pervious hospitalization for heart failure, n (%) 18 (24.7) 9 (42.9) 9 (17.6) 0.0225 Heart failure evolution (days)* 233 (0-1965) 436 (0-3,030) 232 (0-1,647) 0.250 Heart failure evolution (days)* 233 (0-1965) 436 (0-3,030) 232 (0-1,647) 0.250 Easal treatment Furgemente, n (%) 48 (66) 15 (71) 33 (64) 0.654 Ambulatory turnesemide doate* (mg) 40 (0-80) 90 (6-88) 40 (0-60) 0.002 MFA, n (%) 8 (11) 2 (10) 6 (12) 0.583 Thiazides, n (%) 6 (8) 3 (14) 3 (6) 0.345 Acatezolamide, n (%) 2 (2.7) 1 (4.8) 0 (0) 0.049 SLGTZi, n (%) 33 (44) 1 (5) 2 (4) 0.645 PAAS, n (%) 41 (66) 10 (4a) 31 (60) 0.427 Easabockers, n (%) 33 (45) 11 (52) 22 (42) 0.450 Admission Charlson score* 2 (1-3) 2 (2-4) 2 (1-3) 0.212 LVEF (%)* 55 (20-60) 55 (40-60) 0.225 FHFGEF 2 44 (33.6) 7 (33.3) 17 (32.7) - HFGFEF 3 40 (64.7) 12 (67.1) 28 (53.8) - HFGFEF 4 (12.4) 2 (2.6.1) 11 (12.4) 128 (53.8) - HFGFEF 4 (12.4) 2 (2.6.5) 45 (50-65) 45 (50-65) 45 (50-65) 45 (50-55) 45 (50	Atrial Fibrillation, n (%)	43 (58.9)	14 (66.7)	29 (56.9)	0.441
De novo HF, n (%) 226 (55.6) 5 (23.8) 21 (40.4) 0.280 Heat Tables evolution (daya" 230 (0-1965) 436 (0-3.030) 232 (0-1.647) 0.250 Beast treatment Fundsemide, n (%) 48 (66) 15 (71) 33 (64) 0.594 Armbulatory furgemide dose" (mg) 40 (0-60) 0005 (-818) 40 (0-60) 0.032 Armbulatory furgemide dose" (mg) 40 (0-70) 80 (5-818) 40 (0-60) 0.032 Armbulatory furgemide dose" (mg) 41 (156) 12 (10) 66 (12) 0.693 Thackdes, n (%) 6 (8) 3 (14) 3 (6) 0.345 Acatachemide, N(%) 2 (2.7) 1 (4.81 0 0 (0) 0.000 SL 0732, n (%) 3 (4) 1 (5) 2 (4) 0.645 Thackdes, n (%) 31 (45) 11 (52) 22 (42) 0.450 Admission Charlen score" 2 (1-3) 2 (1-3) 0.0 (2.12) HFIGEF 2 44 (33.8) 7 (33.3) 11 (52) 22 (42) 0.450 Admission Charlen score" 2 (1-3) 2 (1-3) 0.212 LVEF (%)* 55 (38-60) 55 (31-69) 55 (40-60) 0.225 HFIGEF 2 44 (33.8) 7 (33.3) 17 (2.7) - HFIGEF 4 0 (04.7) 12 (67.1) 28 (53.8) - TAP85 (ml)* 17 (14-21) 17 (14-21) 0.660 Tricuspid regurgitation lif-V, n (%) 10 (13.7) 2 (0.5) 45 (60-55) 45 (60-56) 42 (55-55) Admission 2 (11) 17 (14-21) 17 (14-21) 0.660 Tricuspid regurgitation lif-V, n (%) 10 (13.7) 2 (0.5) 43 (15-14) 0.714 Systol blood pressure (mmHg)* 141 (123-166) 133 (116-143) 148 (124-175) 0.0443 Systol blood pressure (mmHg)* 141 (123-168) 133 (116-143) 14 (124-175) 0.0443 Systol blood pressure (mmHg)* 86 (6-12) 10 (7-15) 8 (6-51) 0.026 Eleot blood pressure (mmHg)* 86 (-12) 10 (7-15) 8 (6-11) 0.124 Chiothaldone during admission, n (%) 4.0 (5.5) 4 (119) 0 0.0001 Eleote test Eleote test (110) 4.23 (11.0 (-12) 11.0 (-13) 11.0 (13.2 -14.3) 0.014 Chiothaldone (110) admission, n (%) 4.0 (5.5) 4 (110) 7 (128 (12-47) 4.0 (40-76) 0.0244 Chiother (110) (13.7) 12 (10.7-1.4) 4.0 (138 (25-14.4) 0.0144 Chiothaldone (110) admission, n (%) 4.0 (5.5) 4 (119) 0 0.0001 Eleote test (110) 150 (13.5) 11.0 (152.4) 11.0 (132.5-14.4) 0.0144 Chiothaldone (110) (130.7-1.4) 10.0 (132.5-14.4) 0.0244 Chiother (110,01) 12 (12-16) 12 (124.1-15) 130 (122-16) 0.244 Chiother (110,01) 12 (124.1-13) 130 (122-16) 0.244 Chiother (110,01) 12 (14.1-15) 130 (127-16) 0.244	Previous hospitalization for heart failure, n (%)	18 (24.7)	9 (42.9)	9 (17.6)	0.025
Heart failure evolution (days)* 293 (0–1965) 498 (0–3,030) 232 (0–1,647) 0.250 Basis treatment	De novo HF, n (%)	26 (35.6)	5 (23.8)	21 (40.4)	0.280
Basal treatment 48 (66) 15 (71) 33 (64) 0.594 Mabulatory furceenide does ⁶ (mg) 40 (0-80) 80 (5-80) 40 (0-60) 0.032 Mab, n (%) 6 (B) 3 (14) 3 (6) 0.243 Thiazdes, n (%) 6 (B) 3 (14) 3 (6) 0.245 Actanziamidon (%) 2 (2,7) 1 (4.8) 0 (0) 0.049 SLGT2, n (%) 3 (46) 11 (62) 2 2 (42) 0.450 Admission 2 2 (1-5) 2 (2-4) 2 (1-5) 0 (2,27) Charlos score ¹ 2 (1-5) 2 (2-4) 2 (1-5) 0 (22,6) Admission - - - 0 (22,5) Type of HF, n (%) - - - 0 (22,5) HFoEF 9 (12,3) 7 (13,3) - - HFoEF 9 (12,3) 2 (9,5) 7 (13,6) - THASE (mm ^A) 10 (13,7) 2 (8,5) 0 (4,4) 0 (4,4) 0 (4,4) - Systoic blood pressure (mmHg ^A) 16 (6-12)	Heart failure evolution (days) ^a	293 (0–1965)	436 (0–3,030)	232 (0–1,647)	0.250
	Basal treatment				
$\begin{array}{l c c c c c c c c c c c c c c c c c c c$	Furosemide, n (%)	48 (66)	15 (71)	33 (64)	0.594
$\begin{array}{l c c c c c c c c c c c c c c c c c c c$	Ambulatory furosemide dose ^a (mg)	40 (0-80)	80 (5–88)	40 (0–60)	0.032
$\begin{array}{l c c c c c c c c c c c c c c c c c c c$	MRA, n (%)	8 (11)	2 (10)	6 (12)	0.583
Acetazolamich, (%) $2 (2.7)$ 1 (4.8) $0 (0)$ 0.080 SLGT21, n (%) 3 (4) 1 (5) 2 (4) 0.6427 Betablockers, n (%) 33 (45) 11 (52) 22 (42) 0.450 Adrission 2 (1-3) 2 (1-3) 0.212 Def HF, n (%) - - - 0.235 Type of HF, n (%) - - - 0.235 HFrefF 24 (3.3) 7 (33.3) 17 (32.7) - HFrefF 9 (12.3) 2 (9.5) 7 (13.5) - Travesit rmm ⁰ 10 (13.7) 2 (9.5) 7 (13.5) - Travesit rmm ⁰ 17 (14.21) 17 (14.21) 17 (14.21) 0.600 0.227 Systolic blood pressure (mmHg) ^a 46 (54-55) 50 (40-55) 43 (35-55) 0.401 Systolic blood pressure (mmHg) ^a 16 (12-10) 11 (9-12) 0.403 Distolic blood pressure (mmHg) ^a 22 (19-24) 23 (20-25) 22 (19-24) 0.404 Length of staty (dasy) ^a	Thiazides, n (%)	6 (8)	3 (14)	3 (6)	0.345
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Acetazolamide,n (%)	2 (2.7)	1 (4.8)	O (O)	0.080
BAAS, n (%) 41 (56) 10 (43) 31 (60) 0.427 Betablockers, n (%) 33 (45) 11 (52) 22 (42) 0.450 Admission	SLGT2i, n (%)	3 (4)	1 (5)	2 (4)	0.645
Betablockers, n (%) 33 (45) 11 (52) 22 (42) 0.450 Admission Charlson score ^a 2 (1-3) 2 (2-4) 2 (1-3) 0.212 LVEF (%) ^a 55 (38-60) 55 (31-59) 55 (40-60) 0.225 FHGEF 24 (33.8) 7 (33.3) 17 (32.7) - HFmEF 9 (12.3) 2 (9.5) 7 (13.5) - HFmEF 9 (12.4) 12 (57.1) 28 (53.6) - TAPSE (mm) ^a 17 (14-21) 17 (14-21) 0.680. - Trauspict regurgitation III-IV, n (%) 10 (13.7) 2 (9.5) 8 (15.4) 0.714 systolic blood pressure (mmHg) ^a 141 (123-166) 133 (116-148) 148 (124-175) 0.043 Diastolic blood pressure (mmHg) ^a 14 (123-166) 133 (116-148) 148 (124-175) 0.044 Systolic blood pressure (mmHg) ^a 14 (0.69-80) 75 (66-83) 76 (69-80) 0.227 Everest score ^a 11 (0-12) 11 (0-13) 11 (8-12) 0.18 Diastolic blood pressure (mmHg) ^a 8 (6-12) 1	RAASi, n (%)	41 (56)	10 (48)	31 (60)	0.427
Admission Charlson score ^a 2 (1-3) 2 (2-4) 2 (1-3) 0.212 LVEF (%) ^a 55 (38-60) 55 (31-59) 55 (40-60) 0.225 Type of HF, n (%) - - - 0.235 HFmEF 24 (33.8) 7 (3.3) 17 (32.7) - HFmEF 9 (12.3) 2 (9.5) 7 (13.5) - HFmEF 40 (64.7) 12 (67.1) 28 (53.8) - TrAPSE (mm) ^a 17 (14-21) 16 (14-21) 17 (14-21) 0.680 Travspid regurgitation III-IV, n (%) 10 (13.7) 2 (9.5) 8 (15.4) 0.714 Systolic blood pressure (mmHg) ^a 45 (35-55) 50 (40-55) 45 (63-55) 0.491 Systolic blood pressure (mmHg) ^a 76 (69-46) 75 (65-83) 78 (69-90) 0.227 Everest score ^a 11 (9-12) 11 (9-13) 11 (8-12) 0.186 Inferior cava vein (mm) ^a 22 (19-24) 23 (20-26) 22 (19-24) 0.499 Length of stay (days) ^a 8 (6-12) 10 (7-15) 8 (Betablockers, n (%)	33 (45)	11 (52)	22 (42)	0.450
	Admission				
$ \begin{array}{ccccc} LVEF (\%)^{a} & 55 (38-60) & 55 (31-59) & 55 (40-60) & 0.225 \\ Type of HF, n (\%) & - & - & - & 0.235 \\ HrftEF & 24 (33.8) & 7 (33.3) & 17 (32.7) & - \\ HrmtEF & 9 (12.3) & 2 (9.5) & 7 (13.6) & - \\ HFmtEF & 40 (54.7) & 12 (57.1) & 28 (53.8) & - \\ HFpEF & 40 (54.7) & 12 (57.1) & 28 (53.8) & - \\ TAPSE (mm)^{a} & 17 (14-21) & 16 (14-21) & 17 (14-21) & 0.680 \\ Tricuspid regurgitation II-IV, n (\%) & 10 (13.7) & 2 (9.5) & 8 (15.4) & 0.714 \\ sPAP (mmHg)^{a} & 45 (35-55) & 50 (40-55) & 45 (35-55) & 0.491 \\ Systolic blood pressure (mmHg)^{a} & 141 (123-166) & 133 (116-148) & 148 (124-175) & 0.043 \\ Diatolic blood pressure (mmHg)^{a} & 76 (69-66) & 75 (65-83) & 76 (69-90) & 0.227 \\ Everest score^{b} & 11 (9-12) & 11 (9-13) & 11 (8-12) & 0.186 \\ Interior cava vein (mm)^{a} & 22 (19-24) & 23 (20-26) & 22 (19-24) & 0.499 \\ Length of stay (days)^{a} & 8 (6-12) & 10 (7-15) & 8 (5-11) & 0.124 \\ Chlorthaldone during admission, n (\%) & 23.0 (31.5) & 11.0 (52.4) & 12.0 (23.1) & 0.015 \\ Intoropes during admission, n (\%) & 23.0 (31.5) & 11.0 (52.4) & 10 (0.7-14) & 0.032 \\ Sodium (mmol/L)^{a} & 141 (138-143) & 141 (135-143) & 141.00 (138.25-143) & 0.419 \\ Creatinine (mg/d)^{a} & 10 (0.8-1.5) & 1.3 (0.9-2.1) & 1.0 (0.7-1.4) & 0.032 \\ Sodium (mmol/L)^{a} & 4.3 (40-4.9) & 4.2 (40-4.7) & 4.5 (4.0-5.0) & 0.294 \\ Chlorthad (none/L)^{a} & 3.9 (3.7-4.1) & 3.8 (3.5-4.1) & 3.9 (3.7-4.1) & 0.74 \\ Uric acid (g/d)^{a} & 3.9 (3.7-4.1) & 3.8 (3.5-4.1) & 3.9 (3.7-4.1) & 0.74 \\ Hroad (mg/d)^{a} & 13.7 (120-161) & 129 (114-153) & 133 (122-163) & 0.434 \\ Aboterine (mg/d)^{a} & 13.6 (12-161) & 129 (114-153) & 13.0 (12-2-163) & 0.434 \\ Aboterone (mg/d)^{a} & 13.7 (120-161) & 129 (114-153) & 13.0 (122-163) & 0.434 \\ Aboterone (mg/d)^{b} & 13.7 (120-161) & 129 (114-153) & 13.0 (122-163) & 0.434 \\ Aboterone (mg/d)^{b} & 13.7 (120-161) & 129 (114-153) & 13.0 (122-163) & 0.434 \\ Aboterone (mg/d)^{b} & 13.7 (120-161) & 129 (114-153) & 13.0 (122-163) & 0.434 \\ Aboterone (mg/d)^{b} & 11.5 (7.3-18.0) & 15.1 (10.7-4.3) & 9.7 (6.8-14.2) & 0.004 \\ Abornoli$	Charlson score ^a	2 (1–3)	2 (2-4)	2 (1-3)	0.212
Type of HF, n (%) - - - 0.235 HFREF 24 (33.8) 7 (33.3) 17 (32.7) - HFREF 9 (12.3) 2 (9.5) 7 (13.5) - HFREF 40 (54.7) 12 (57.1) 28 (53.8) - TAPSE (mm) ^a 17 (14-21) 16 (14-21) 17 (14-21) 0.680 Tricuspid regurgitation III-IV, n (%) 10 (13.7) 2 (9.5) 8 (15.4) 0.714 sPAP (mmHg) ^a 45 (35-55) 50 (40-55) 45 (35-55) 0.491 Systolic blood pressure (mmHg) ^a 14 (123-166) 133 (116-148) 148 (124-175) 0.043 Diastolic blood pressure (mmHg) ^a 28 (69-66) 75 (66-83) 76 (69-90) 0.227 Everest score ^a 11 (9-12) 11 (9-13) 11 (8-12) 0.186 Inferior cava vein (mm) ^a 22 (19-24) 23 (20-26) 22 (19-24) 0.499 Length of stay (days) ^a 8 (6-12) 10 (7-15) 8 (5-11) 0.118 Interior cava vein (mm) ^a 23.0 (31.5) 11.0 (52.4) 12.0 (23.1) 0.001 Bood tests 57.2 (41.9-84.5) 49.3 (28.0-63	LVEF (%) ^a	55 (38–60)	55 (31–59)	55 (40-60)	0.225
HrtEF 24 (33.8) 7 (33.3) 17 (32.7) - HFmtFF 9 (12.3) 2 (9.5) 7 (13.5) - TAPSE (mm) ⁶ 17 (14-21) 16 (14-21) 17 (14-21) 0.680 Trouspid regurgitation III-IV, n (%) 10 (13.7) 2 (9.5) 8 (15.4) 0.71 SPAP (mmHg) ^a 45 (35-55) 50 (40-55) 45 (35-55) 0.491 Systolic blood pressure (mmHg) ^a 141 (123-166) 133 (116-148) 148 (124-175) 0.043 Diastolic blood pressure (mmHg) ^a 16 (69-86) 75 (65-63) 76 (69-90) 0.227 Everest score ^a 11 (9-12) 11 (9-13) 11 (8-12) 0.186 Inferior cava vein (mm) ^a 22 (19-24) 23 (20-26) 22 (19-24) 0.499 Length of stay (days) ^a 8 (6-12) 10 (7-15) 8 (5-11) 0.127 Inotropes during admission, n (%) 23.03 (15.5) 11.0 (62.4) 12.0 (23.1) 0.015 Inotropes during admission, n (%) 43.0 (4077.5) 74.0 (50.5-80.5) 51 (40-75) 0.044 Urea (mg/d) ^b <td< td=""><td>Type of HF. n (%)</td><td>_</td><td>_</td><td>_</td><td>0.235</td></td<>	Type of HF. n (%)	_	_	_	0.235
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	HFrEF	24 (33.8)	7 (33.3)	17 (32.7)	_
HFpEF40 (64.7)12 (67.1)28 (63.8)-TAPSE (mm) ⁶ 17 (14-21)16 (14-21)17 (14-21)0.680Tricuspid regurgitation III-IV, n (%)10 (13.7)2 (9.5)8 (15.4)0.714SPAP (mmHg) ^a 45 (35-55)50 (40-55)45 (35-55)0.491Systolic blood pressure (mmHg) ^a 141 (123-166)133 (116-148)148 (124-175)0.043Diastolic blood pressure (mmHg) ^a 76 (69-86)75 (65-83)76 (69-90)0.227Everest score ^a 11 (9-12)11 (9-13)11 (8-12)0.186Inferior cava vein (mm) ^a 22 (19-24)23 (20-26)22 (19-24)0.499Length of stay (days) ^a 8 (6-12)10 (7-15)8 (5-11)0.124Chlorthalidone during admission, n (%)23.0 (31.5)11.0 (52.4)12.0 (23.1)0.015Inotropes during admission, n (%)4.0 (5.5)4 (19)00.001Blood testsGiomerular filtration ml/min/1.73 m ^{2a} 57.2 (41.9-84.5)1.3 (0.9-2.1)1.0 (0.7-1.4)0.032Sodium (mmol/L) ^a 141 (138-143)141 (138-143)141.00 (138.25-143)0.419Potassium (mmol/L) ^a 143 (4.0-4.7)4.5 (4.0-5.0)0.294Chloride (grolf) ^a 8.2 (7.0-9.1)8.2 (7.0-9.1)8.2 (7.0-9.1)0.62 (4.1-96.2)0.044Urea (mg/df) ^a 10.5 (0.3-107)10.4 (101-106)105 (103-107)0.074Urea (mg/df) ^a 1.2 (7.0-9.1)8.2 (7.0-9.1)8.2 (7.0-9.1)8.2 (7.0-9.1)0.2 (4.0-4.7)4.5 (4.0-5.0)	HEmrEE	9 (12.3)	2 (9.5)	7 (13.5)	_
TAPSE (mm) ^a 17 (14-21)16 (14-21)17 (14-21)0.680Tricuspid regurgitation III-IV, n (%)10 (13.7)2 (9.5)8 (15.4)0.714sPAP (mmHg) ^a 45 (35-55)50 (40-55)45 (35-55)0.491Systolic blood pressure (mmHg) ^a 141 (123-166)133 (116-148)1148 (124-175)0.043Diastolic blood pressure (mmHg) ^a 76 (69-86)75 (65-83)76 (69-90)0.227Everest score ^a 11 (9-12)11 (9-13)11 (8-12)0.186Inferior cave vein (mm) ^a 22 (19-24)23 (20-26)22 (19-24)0.499Length of stay (days) ^a 8 (6-12)10 (7-15)8 (5-11)0.124Chlorthalidone during admission, n (%)23.0 (31.5)11.0 (52.4)12.0 (23.1)0.015Inotropes during admission, n (%)4.0 (5.5)4.93 (28.0-63.2)69.4 (44.1-86.2)0.044Urea (mg/d1) ^a 10 (0.8-1.5)1.3 (0.9-2.1)1.0 (0.7-1.4)0.032Sodium (mmol/L) ^a 4.3 (4.0-4.9)4.2 (4.0-4.7)4.5 (4.0-5.0)0.294Chloride (mmol/L) ^a 105 (103-107)104 (101-106)105 (103-107)0.074Vir caveli (g/d1) ^a 5.691 (2.447-9731)7583 (3.421-11944)5.039 (1976-9368)0.165Ca 125 (U/m1) ^a 62 (20-128)57 (9-159)62 (24-127)0.606NT-proENP (pg/m1) ^a 5.691 (2.447-9731)7583 (3.421-11944)5.039 (1976-9368)0.165Ca 125 (U/m1) ^a 137 (120-161)129 (114-153)139 (122-163)0.434Aldosterone (ng/d1) ^a </td <td>HEDEE</td> <td>40 (54.7)</td> <td>12 (57.1)</td> <td>28 (53.8)</td> <td>_</td>	HEDEE	40 (54.7)	12 (57.1)	28 (53.8)	_
Tricuspic regurgitation III-IV, n (%) TO (13.7) 2 (9.5) 8 (15.4) 0.714 sPAP (mmHg) ^a 45 (35-55) 50 (40-55) 45 (35-55) 0.491 Systolic blood pressure (mmHg) ^a 141 (123-166) 133 (116-148) 148 (124-175) 0.043 Diastolic blood pressure (mmHg) ^a 76 (69-86) 75 (65-83) 76 (69-90) 0.227 Everest score ^a 11 (9-12) 11 (9-13) 11 (8-12) 0.186 Inferior cava vein (mm) ^a 22 (19-24) 23 (20-26) 22 (19-24) 0.499 Length of stay (days) ^a 8 (6-12) 10 (7-15) 8 (5-11) 0.124 Chlorthalidone during admission, n (%) 2.30 (31.5) 11.0 (52.4) 12.0 (23.1) 0.001 Blood tests E 57.2 (41.9-84.5) 49.3 (28.0-63.2) 69.4 (44.1-86.2) 0.044 Urea (mg/d) ^a 50.0 (41.0-77.5) 74.0 (50.5-80.5) 51 (40-75) 0.044 Creatinine (mg/d) ^a 1.0 (0.8-1.5) 1.3 (0.9-2.1) 1.0 (0.7-1.4) 0.032 Sodium (mmol/L) ^a 141 (138-143) 141 (135-143) 141.00 (138.25-143) 0.419 Potassium (mmol/L) ^a 1.43 (4.0-4	TAPSE (mm) ^a	17 (14-21)	16 (14–21)	17 (14–21)	0.680
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Tricuspid requiration III-IV n (%)	10 (13 7)	2 (9 5)	8 (15 4)	0.000
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	sPAP (mmHa) ^a	45 (35-55)	50 (40-55)	45 (35-55)	0.491
Option block (mm/g) TH (120-160) The (12-160) The (12-160) Class (12-176) Class (1	Systelic blood pressure (mmHa) ^a	141 (123–166)	133 (116–148)	148 (124–175)	0.043
Disability Dides bitsTro (05-00)Tro (05-00)Display (05-00) 0.221 Everest score ^a 11 (9-12)11 (9-12)11 (9-12)0Inferior cava vein (mm) ^a 22 (19-24)23 (20-26)22 (19-24)0.499Length of stay (days) ^a 8 (6-12)10 (7-15)8 (5-11)0.124Chlorthalidone during admission, n (%)23.0 (31.5)11.0 (52.4)12.0 (23.1)0015Inotropes during admission, n (%)4.0 (5.5)4 (19)00Blood testsGiomerular filtration ml/min/1.73 m ^{2a} 57.2 (41.9-84.5)49.3 (28.0-63.2)69.4 (44.1-86.2)0.044Urea (mg/dl) ^a 56.0 (41.0-77.5)74.0 (50.5-80.5)51 (40-75)0.044Creatinine (mg/dl) ^a 1.0 (0.8-1.5)1.3 (0.9-2.1)1.0 (0.7-1.4)0.032Sodium (mmol/L) ^a 141 (138-143)141 (135-143)141.00 (138.25-143)0.419Potassium (mmol/L) ^a 4.3 (4.0-4.9)4.2 (4.0-4.7)4.5 (4.0-5.0)0.294Chloride (mmol/L) ^a 105 (103-107)104 (101-106)105 (103-107)0.074Uric acid (g/dl) ^a 8.2 (7.0-9.1)8.2 (7.0-9.1)8.2 (6.4-9.1)0.749NT-proBNP (gg/ml) ^a 5.691 (2.447-9731)7583 (3.421-11944)5.039 (1976-9368)0.165Ca 125 (U/ml) ^a 3.9 (3.7-4.1)3.8 (3.5-4.1)3.9 (3.7-4.1)0.213Cholesterol(mg/dl) ^a 13.7 (120-161)129 (114-153)139 (122-163)0.434Adosterone (ng/dl) ^a 13.7 (120-161)129 (114-153)139 (122-163)	Diastolic blood pressure (mmHa) ^a	76 (60, 86)	75 (65 83)	76 (60, 00)	0.043
Levelse Softe11 (g-12)11 (g-12)11 (g-12)0.160Inferior cava vein (mm) ^a 22 (19–24)23 (20–26)22 (19–24)0.499Length of stay (days) ^a 8 (6–12)10 (7–15)8 (5–11)0.124Chlorthalidone during admission, n (%)23.0 (31.5)11.0 (52.4)12.0 (23.1)0.015Inotropes during admission, n (%)4.0 (5.5)4 (19)000.001Blood testsGlomerular filtration ml/min/1.73 m ^{2a} 57.2 (41.9–84.5)49.3 (28.0–63.2)69.4 (44.1–86.2)0.044Urea (mg/dl) ^a 56.0 (41.0–77.5)74.0 (50.5–80.5)51 (40–75)0.044Urea (mg/dl) ^a 1.0 (0.8–1.5)1.3 (0.9–2.1)1.0 (0.7–1.4)0.032Sodium (mmol/L) ^a 141 (138–143)141 (135–143)141.00 (138.25–143)0.419Potassium (mmol/L) ^a 4.3 (4.0–4.9)4.2 (4.0–4.7)4.5 (4.0–5.0)0.294Chloride (mmol/L) ^a 105 (103–107)104 (101–106)105 (103–107)0.074Uric acid (g/dl) ^a 8.2 (7.0–11)8.2 (6.4–9.1)0.749NT-proBNP (pg/ml) ^a 5,691 (2.447–9731)7583 (3.421–11944)5,039 (1976–9368)0.165Ca 125 (U/ml) ^a 3.9 (3.7–4.1)3.8 (3.5–4.1)3.9 (3.7–4.1)0.213Cholesterol(mg/dl) ^a 13.7 (120–161)12.9 (114–153)13.9 (122–163)0.434Albumin (g/dl) ^a 13.7 (120–161)12.8 (11.7–14.6)0.034Albumin (g/dl) ^a 13.7 (120–161)12.8 (10.9–14.0)12.8 (11.7–14.6)0.035 <td>Everent approa</td> <td>11 (0, 12)</td> <td>11 (0, 12)</td> <td>11 (9 10)</td> <td>0.227</td>	Everent approa	11 (0, 12)	11 (0, 12)	11 (9 10)	0.227
Interfor Cava Veril (Init) $22 (19-24)$ $23 (20-20)$ $22 (19-24)$ 0.499 Length of stay (days) ^a 8 (6-12)10 (7-15)8 (5-11)0.124Chlorthalidone during admission, n (%) $23.0 (31.5)$ 11.0 (52.4)12.0 (23.1)00Inotropes during admission, n (%) $4.0 (5.5)$ $4 (19)$ 00Blood testsGiomerular filtration ml/min/1.73 m ^{2a} $57.2 (41.9-84.5)$ $49.3 (28.0-63.2)$ $69.4 (44.1-86.2)$ 0.0444 Urea (mg/dl) ^a $56.0 (41.0-77.5)$ $74.0 (50.5-80.5)$ $51 (40-75)$ 0.0444 Creatinine (mg/dl) ^a $1.0 (0.8-1.5)$ $1.3 (0.9-2.1)$ $1.0 (0.7-1.4)$ 0.032 Sodium (mmol/L) ^a 141 (138-143)141 (135-143)141.00 (138.25-143) 0.419 Potassium (mmol/L) ^a 4.3 (4.0-4.9) $4.2 (4.0-4.7)$ $4.5 (4.0-5.0)$ 0.294 Chloride (mmol/L) ^a $8.2 (7.0-9.1)$ $8.2 (7.0-10.1)$ $8.2 (6.4-9.1)$ 0.74 NT-proBNP (pg/ml) ^a $5,691 (2,447-9731)$ $7583 (3,421-11944)$ $5,039 (1976-9368)$ 0.165 Ca 125 (U/ml) ^a $3.9 (3.7-4.1)$ $3.8 (3.5-4.1)$ $3.9 (3.7-4.1)$ 0.213 Albumin (g/dl) ^a $11.5 (7.3-18.0)$ $19.1 (10.7-40.3)$ $9.7 (6.8-14.2)$ 0.094 Albumin (g/dl) ^a $12.8 (11.2-14.5)$ $12.8 (10.9-14.0)$ $12.8 (11.2-14.6)$ 0.394	Inferior aqua vain (mm) ^a	11(9-12)	11 (9-13)	11(0-12)	0.100
Left Di Stay (Days) $3 (6^{-12})$ $10 (7^{-15})$ $3 (5^{-11})$ 0.124 Chlorthalidone during admission, n (%)23.0 (31.5)11.0 (52.4)12.0 (23.1) 0.015 Inotropes during admission, n (%) $4.0 (5.5)$ $4 (19)$ 0 0.001 Blood testsGlomerular filtration ml/min/1.73 m ^{2a} $57.2 (41.9-84.5)$ $49.3 (28.0-63.2)$ $69.4 (44.1-86.2)$ 0.044 Urea (mg/dl) ^a $56.0 (41.0-77.5)$ $74.0 (50.5-80.5)$ $51 (40-75)$ 0.044 Creatinine (mg/dl) ^a $1.0 (0.8-1.5)$ $1.3 (0.9-2.1)$ $1.0 (0.7-1.4)$ 0.032 Sodium (mmol/L) ^a $141 (138-143)$ $141 (135-143)$ $141.00 (138.25-143)$ 0.419 Potassium (mmol/L) ^a $4.3 (4.0-4.9)$ $4.2 (4.0-4.7)$ $4.5 (4.0-5.0)$ 0.294 Chloride (mmol/L) ^a $105 (103-107)$ $104 (101-106)$ $105 (103-107)$ 0.074 Uric acid (g/dl) ^a $8.2 (7.0-9.1)$ $8.2 (7.0-9.1)$ $8.2 (6.4-9.1)$ 0.749 NT-proBNP (pg/ml) ^a $5.691 (2.447-9731)$ $7583 (3.421-11944)$ $5.039 (1976-9368)$ 0.165 Ca 125 (U/ml) ^a $3.9 (3.7-4.1)$ $3.8 (3.5-4.1)$ $3.9 (3.7-4.1)$ 0.213 Albumin (g/dl) ^a $137 (120-161)$ $129 (114-153)$ $139 (122-163)$ 0.434 Aldosterone (ng/dl) ^a $11.5 (7.3-18.0)$ $19.1 (10.7-40.3)$ $9.7 (6.8-14.2)$ 0.005	linenor cava veni (min)	22 (19-24)	23 (20-20)	22 (19-24)	0.499
Chlorthaldone during admission, n (%)23.0 (31.5)11.0 (52.4)12.0 (23.1)0.015Inotropes during admission, n (%)4.0 (5.5)4 (19)000.001Blood testsGiomerular filtration ml/min/1.73 m ^{2a} 57.2 (41.9–84.5)49.3 (28.0–63.2)69.4 (44.1–86.2)0.044Urea (mg/dl) ^a 56.0 (41.0–77.5)74.0 (50.5–80.5)51 (40–75)0.044Creatinine (mg/dl) ^a 1.0 (0.8–1.5)1.3 (0.9–2.1)1.0 (0.7–1.4)0.032Sodium (mmol/L) ^a 141 (138–143)141 (135–143)141.00 (138.25–143)0.419Potassium (mmol/L) ^a 105 (103–107)104 (101–106)105 (103–107)0.074Uric acid (g/dl) ^a 8.2 (7.0–9.1)8.2 (7.0–10.1)8.2 (6.4–9.1)0.749NT-proBNP (pg/ml) ^a 5,691 (2,447–9731)7583 (3,421–11944)5,039 (1976–9368)0.165Ca 125 (U/ml) ^a 3.9 (3.7–4.1)3.9 (3.7–4.1)3.9 (3.7–4.1)0.213Chlorider (mg/dl) ^a 137 (120–161)129 (114–153)139 (122–163)0.444Aldosterone (ng/dl) ^a 11.5 (7.3–18.0)19.1 (10.7–40.3)9.7 (6.8–14.2)0.005	Oblasta slidara al miana administrational (%)	8 (0-12)	10 (7-15)	10 0 (00 1)	0.124
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Blood testsGlomerular filtration ml/min/1.73 m2a $57.2 (41.9-84.5)$ $49.3 (28.0-63.2)$ $69.4 (44.1-86.2)$ 0.044 Urea (mg/dl) ^a $56.0 (41.0-77.5)$ $74.0 (50.5-80.5)$ $51 (40-75)$ 0.044 Creatinine (mg/dl) ^a $1.0 (0.8-1.5)$ $1.3 (0.9-2.1)$ $1.0 (0.7-1.4)$ 0.032 Sodium (mmol/L) ^a $141 (138-143)$ $141 (135-143)$ $141.00 (138.25-143)$ 0.419 Potassium (mmol/L) ^a $4.3 (4.0-4.9)$ $4.2 (4.0-4.7)$ $4.5 (4.0-5.0)$ 0.294 Chloride (mmol/L) ^a $105 (103-107)$ $104 (101-106)$ $105 (103-107)$ 0.074 Uric acid (g/dl) ^a $8.2 (7.0-9.1)$ $8.2 (7.0-10.1)$ $8.2 (6.4-9.1)$ 0.749 NT-proBNP (pg/ml) ^a $5,691 (2,447-9731)$ $7583 (3,421-11944)$ $5,039 (1976-9368)$ 0.165 Ca 125 (U/ml) ^a $3.9 (3.7-4.1)$ $3.8 (3.5-4.1)$ $3.9 (3.7-4.1)$ 0.213 Cholesterol(mg/dl) ^a $137 (120-161)$ $129 (114-153)$ $139 (122-163)$ 0.434 Aldosterone (ng/dl) ^a $12.8 (11.3-14.5)$ $19.1 (10.7-40.3)$ $9.7 (6.8-14.2)$ 0.005	inotropes during admission, n (%)	4.0 (5.5)	4 (19)	U	0.001
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Potassium (mmol/L)a $4.3 (4.0-4.9)$ $4.2 (4.0-4.7)$ $4.5 (4.0-5.0)$ 0.294 Chloride (mmol/L)a $105 (103-107)$ $104 (101-106)$ $105 (103-107)$ 0.074 Uric acid (g/dl)a $8.2 (7.0-9.1)$ $8.2 (7.0-10.1)$ $8.2 (6.4-9.1)$ 0.749 NT-proBNP (pg/ml)a $5,691 (2,447-9731)$ $7583 (3,421-11944)$ $5,039 (1976-9368)$ 0.165 Ca 125 (U/ml)a $62 (20-128)$ $57 (9-159)$ $62 (24-127)$ 0.606 Albumin (g/dl)a $3.9 (3.7-4.1)$ $3.8 (3.5-4.1)$ $3.9 (3.7-4.1)$ 0.213 Cholesterol(mg/dl)a $137 (120-161)$ $129 (114-153)$ $139 (122-163)$ 0.434 Aldosterone (ng/dl)a $11.5 (7.3-18.0)$ $19.1 (10.7-40.3)$ $9.7 (6.8-14.2)$ 0.005 Hemoglobin (g/dl)a $12.8 (11.3-14.5)$ $12.8 (10.9-14.0)$ $12.8 (11.7-14.6)$ 0.394	Sodium (mmol/L) ^a	141 (138–143)	141 (135–143)	141.00 (138.25–143)	0.419
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Uric acid (g/dl) ^a 8.2 (7.0–9.1)8.2 (7.0–10.1)8.2 (6.4–9.1)0.749NT-proBNP (pg/ml) ^a 5,691 (2,447–9731)7583 (3,421–11944)5,039 (1976–9368)0.165Ca 125 (U/ml) ^a 62 (20–128)57 (9–159)62 (24–127)0.606Albumin (g/dl) ^a 3.9 (3.7–4.1)3.8 (3.5–4.1)3.9 (3.7–4.1)0.213Cholesterol(mg/dl) ^a 137 (120–161)129 (114–153)139 (122–163)0.434Aldosterone (ng/dl) ^a 11.5 (7.3–18.0)19.1 (10.7–40.3)9.7 (6.8–14.2)0.005Hemoglobin (g/dl) ^a 12.8 (11.3–14.5)12.8 (10.9–14.0)12.8 (11.7–14.6)0.394	Chloride (mmol/L) ^a	105 (103–107)	104 (101–106)	105 (103–107)	0.074
NT-proBNP (pg/ml) ^a 5,691 (2,447-9731) 7583 (3,421-11944) 5,039 (1976-9368) 0.165 Ca 125 (U/ml) ^a 62 (20-128) 57 (9-159) 62 (24-127) 0.606 Albumin (g/dl) ^a 3.9 (3.7-4.1) 3.8 (3.5-4.1) 3.9 (3.7-4.1) 0.213 Cholesterol(mg/dl) ^a 137 (120-161) 129 (114-153) 139 (122-163) 0.434 Aldosterone (ng/dl) ^a 11.5 (7.3-18.0) 19.1 (10.7-40.3) 9.7 (6.8-14.2) 0.005 Hemoglobin (g/dl) ^a 12.8 (11.3-14.5) 12.8 (10.9-14.0) 12.8 (11.7-14.6) 0.394	Uric acid (g/dl) ^a	8.2 (7.0–9.1)	8.2 (7.0–10.1)	8.2 (6.4–9.1)	0.749
Ca 125 $(U/m)^a$ 62 $(20-128)$ 57 $(9-159)$ 62 $(24-127)$ 0.606Albumin $(g/d)^a$ $3.9 (3.7-4.1)$ $3.8 (3.5-4.1)$ $3.9 (3.7-4.1)$ 0.213Cholesterol(mg/dl)^a $137 (120-161)$ $129 (114-153)$ $139 (122-163)$ 0.434Aldosterone $(ng/dl)^a$ $11.5 (7.3-18.0)$ $19.1 (10.7-40.3)$ $9.7 (6.8-14.2)$ 0.005 Hemoglobin $(g/dl)^a$ $12.8 (11.3-14.5)$ $12.8 (10.9-14.0)$ $12.8 (11.7-14.6)$ 0.394	NT-proBNP (pg/ml) ^a	5,691 (2,447–9731)	7583 (3,421–11944)	5,039 (1976–9368)	0.165
Albumin (g/dl) ^a 3.9 (3.7-4.1) 3.8 (3.5-4.1) 3.9 (3.7-4.1) 0.213 Cholesterol(mg/dl) ^a 137 (120-161) 129 (114-153) 139 (122-163) 0.405 Aldosterone (ng/dl) ^a 11.5 (7.3-18.0) 19.1 (10.7-40.3) 9.7 (6.8-14.2) 0.005 Hemoglobin (a/dl) ^a 12.8 (11.3-14.5) 12.8 (10.9-14.0) 12.8 (11.7-14.6) 0.394	Ca 125 (U/ml) ^a	62 (20–128)	57 (9–159)	62 (24–127)	0.606
Cholesterol(mg/dl) ^a 137 (120–161) 129 (114–153) 139 (122–163) 0.430 Aldosterone (ng/dl) ^a 11.5 (7.3–18.0) 19.1 (10.7–40.3) 9.7 (6.8–14.2) 0.005 Hemoglobin (a/dl) ^a 12.8 (11.3–14.5) 12.8 (10.9–14.0) 12.8 (11.7–14.6) 0.394	Albumin (q/dl) ^a	3.9 (3.7–4.1)	38 (35-41)	3.9 (3.7–4.1)	0.213
Aldosteron (ng/dl) ^a 11.5 (7.3–18.0) 19.1 (10.7–40.3) 9.7 (6.8–14.2) 0.004 Hemoglobin (a/dl) ^a 12.8 (11.3–14.5) 12.8 (10.9–14.0) 12.8 (11.7–14.6) 0.304	Cholesterol(mg/dl) ^a	137 (120–161)	129 (114-153)	139 (122–163)	0.210
Hemoglobin $(n/d)^a$ 12.8 (11.3–14.5) 12.8 (10.9–14.0) 12.8 (11.7–14.6) 0.394	Aldosterone (ng/dl) ^a	11.5 (7.3–18.0)	19.1 (10.7–40.3)	9.7 (6.8–14.2)	0.404
	Hemoglobin (g/dl) ^a	12.8 (11 3–14 5)	12.8 (10.9–14.0)	12.8 (11 7–14 6)	0.394

DR, diuretic response; MRA, mineralocorticoids receptor antagonists; SLGT2i, Sodium–glucose cotransporter 2 inhibitors; RAASi, Renin-angiotensin-aldosterone system inhibitors; LVEF, left ventricular ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrFF, heart failure with reduced ejection fraction; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; NTproBNP, N-terminal pro-brain natriuretic peptide; CA125, cancer antigen 125. Bold type: statistically significant values.

^aContinous variables are expressed by medians and interquartile range.

These patients showed some characteristics traditionally described in patients with diuretic resistance in other settings.

Natriuresis and Diuresis in Acute Heart Failure

Sodium and fluid retention is a hallmark of HF. As effective diuretic response is produced by natriuresis, urinary sodium has emerged as a useful parameter to predict natriuretic response in patients with HF soon after diuretic administration (Verbrugge et al., 2014), which can be measured from a urinary spot sample with good accuracy (Testani et al., 2016). In this line, several studies have reported the usefulness of natriuresis after the first dose of diuretic to predict long-term adverse events (Singh et al., 2014; Honda et al., 2018; Luk et al., 2018; Biegus et al., 2019; Hodson et al., 2019), and two studies have also suggested its usefulness in detecting the development of worsening HF during hospitalization (Collins et al., 2019; Cobo -Marcos et al., 2020).

Although a high diuresis volume following a first intravenous loop diuretic administration is usually associated with good diuretic response and a high urinary sodium (Testani et al., 2016; Singh et al., 2014), some data indicate that in patients with low to medium volume output, spot urinary sodium content offers independent prognostic information (Brinkley et al., 2018). Indeed, in our cohort only 4 patients (5.5%) had both low urinary sodium and a decreased urine output.

Therefore, a spot urine sodium content of <50-70 mEq/L after 2 h, and/or an hourly urine output <100-150 ml during the first 6 h, provide additional information and could identify patients with an insufficient diuretic response.

Characteristics of Patients With Insufficient Diuretic Response

The present study confirms findings from previous studies, that a poor response is associated with some features of more advanced disease (Metra et al., 2012; Neuberg et al., 2002; Valente et al., 2014; ter Maaten et al., 2015b; Testani et al., 2014; Voors et al., 2014; ter Maaten et al., 2015a). In our cohort 43% of the patients had a previous HF hospitalization, and the outpatient diuretic dose was high. Besides, compared with patients with an adequate diuretic response, these patients had lower systolic blood pressure at admission, worse glomerular filtration rate, and showed greater neurohormonal activation. It should be noted that variables such as age, left ventricular ejection fraction or natriuretic peptides are not usually associated with the diuretic response in different studies (Metra et al., 2012; Neuberg et al., 2002; Valente et al., 2014; ter Maaten et al., 2015b; Testani et al., 2014; Voors et al., 2014; ter Maaten et al., 2015a). Furthermore, in our cohort no other clinical (Charlson index, Everest score) or echocardiogram features (TAPSE, inferior cava vein) were different between both populations. These data highlight the role of this algorithm in the evaluation of diuretic response in this setting.

Finally, although this study didn't assess long term events, we showed that patients with a worse diuretic response required diuretic association and inotropes more frequently during admission.

Feasibility of the ESC Algorithm

At this time, two other studies are evaluating the performance of this diagnostic strategy, the ENACT-HF trial (Rationale and Design of the Efficacy of a Standardized Diuretic Protocol in Acute Heart Failure Study) (Dauw et al., 2021), and the PUSH-HF trial (Natriuresis-guided therapy in acute heart failure: rationale and design of the Pragmatic Urinary Sodium-based treatment algoritHm in Acute Heart) (Maaten et al., 2022).

It should be noted that this novel algorithm involves a more proactive approach and closer monitoring of the diuretic response.

This requires specific training and coordinated and continuos collaboration between the professionals involved in the management of HF patients, especially with emergency department staff, in order to extend the implementation of this diuretic protocol.

Limitations

Our cohort consisted of 73 patients from one academic institution so the findings may not be generalizable to the wider acute HF population.

In addition, there is a low percentage of patients included (11%) in terms of overall acute HF admissions. Patients with predominantly pulmonary congestion without other congestion signs were not included. Some patients didn't follow the protocol by decision of the responsible staff. Recruitment was also affected by the COVID-19 pandemic.

CONCLUSION

The diagnostic algorithm based on diuresis and natriuresis provided complementary information and was capable of early detection of up to 29% of patients with acute HF from this cohort who presented an insufficient diuretic response.

This finding may help to stratify patients who may benefit from more intense treatment for decongestion during hospital admission.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Comité de Ética e Investigación con Medicamentos (CEIm) del Hospital Puerta de Hierro Majadahonda. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MC-M, FD, PG-P and JS contributed to conception and design of the study. AiM, MM, AS, and CG, contributed to

the patient inclusion. DD, PM, FT, RG, AnM, and DE contributed to the data inclusion on the database. AG organized the laboratory tests. MC-M organized the database. BG-M performed the statistical analysis. BG-M and EH wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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