Circulation: Heart Failure

ORIGINAL ARTICLE

Protocolized Natriuresis-Guided Decongestion Improves Diuretic Response: The Multicenter ENACT-HF Study

Jeroen Dauw, MD, MMed; Kristina Charaya, MD, PhD; Małgorzata Lelonek, MD, PhD; Isabel Zegri-Reiriz, MD, PhD; Samer Nasr, MD; Cynthia P. Paredes-Paucar, MD; Attila Borbély, MD, PhD; Fatih Erdal, MD; Riad Benkouar, MD, PhD; Marta Cobo-Marcos, MD; Gonzalo Barge-Caballero, MD, PhD; Varghese George, MD, DMM; Cornelia Zara, MD; Noel T. Ross, MD; Diane Barker, MD; Annop Lekhakul, MD; Simone Frea, MD; Azmee M. Ghazi, MD; Dorit Knappe, MD; Nawal Doghmi, MD; Milka Klincheva, MD, PhD; Inês Fialho, MD; Virginia Bovolo, MD; Hajo Findeisen, MD; Imad A. Alhaddad, MD; Alessandro Galluzzo, MD; Rafael de la Espriella, MD; Ramzi Tabbalat, MD; Òscar Miró, MD, PhD; Jagdeep S. Singh, MBBS, MD; Petra Nijst, MD, PhD; Matthias Dupont, MD; Pieter Martens, MD, PhD; Wilfried Mullens, MD, PhD

BACKGROUND: The use of urinary sodium to guide diuretics in acute heart failure is recommended by experts and the most recent European Society of Cardiology guidelines. However, there are limited data to support this recommendation. The ENACT-HF study (Efficacy of a Standardized Diuretic Protocol in Acute Heart Failure) investigated the feasibility and efficacy of a standardized natriuresis-guided diuretic protocol in patients with acute heart failure and signs of volume overload.

METHODS: ENACT-HF was an international, multicenter, open-label, pragmatic, 2-phase study, comparing the current standard of care of each center with a standardized diuretic protocol, including urinary sodium to guide therapy. The primary end point was natriuresis after 1 day. Secondary end points included cumulative natriuresis and diuresis after 2 days of treatment, length of stay, and in-hospital mortality. All end points were adjusted for baseline differences between both treatment arms.

RESULTS: Four hundred one patients from 29 centers in 18 countries worldwide were included in the study. The natriuresis after 1 day was significantly higher in the protocol arm compared with the standard of care arm (282 versus 174 mmol; adjusted mean ratio, 1.64; $P<0.001$). After 2 days, the natriuresis remained higher in the protocol arm (538 versus 365 mmol; adjusted mean ratio, 1.52; $P<0.001$), with a significantly higher diuresis (5776 versus 4381 mL; adjusted mean ratio, 1.33; $P<0.001$). The protocol arm had a shorter length of stay (5.8 versus 7.0 days; adjusted mean ratio, 0.87; $P=0.036$). In-hospital mortality was low and did not significantly differ between the 2 arms (1.4% versus 2.0%; $P=0.852$).

CONCLUSIONS: A standardized natriuresis-guided diuretic protocol to guide decongestion in acute heart failure was feasible, safe, and resulted in higher natriuresis and diuresis, as well as a shorter length of stay.

Key Words: diuretics ■ heart failure ■ length of stay ■ natriuresis ■ sodium

See Editorial by Felker

Congestion is a hallmark sign of acute heart failure (AHF) and is a leading cause for hospitalization in heart failure patients.[1] According to both the European Society of Cardiology and American Heart Association/American College of Cardiology/Heart Failure Society of America guidelines, diuretics are recommended

Correspondence to: Jeroen Dauw, MD, MMed, and Wilfried Mullens, MD, PhD, Department of Cardiology, Ziekenhuis Oost-Limburg, Schiepse Bos 6, 3600 Genk, Belgium. Email jeroen.dauw@zol.be and wilfried.mullens@zol.be
Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCHEARTFAILURE.123.011105.
For Sources of Funding and Disclosures, see page 10.

Circulation: Heart Failure is available at www.ahajournals.org/journal/circheartfailure

WHAT IS NEW?

- Current European Society of Cardiology guidelines recommend the use of urinary sodium to guide decongestion in acute heart failure, but there are limited data to support this strategy.
- The ENACT-HF study (Efficacy of a Standardized Diuretic Protocol in Acute Heart Failure) was a prospective, nonrandomized, open-label, 2-phase study in 29 centers across 18 countries comparing each center's standard of care with a standardized natriuresis-guided diuretic protocol.
- The protocol was associated with a 64% higher natriuresis within the first day of treatment and a sustained higher diuresis and natriuresis during the first 2 days. Length of stay was 1 day shorter in the protocol arm.

WHAT ARE THE CLINICAL IMPLICATIONS?

- The ENACT-HF study results support the use of urinary sodium to guide decongestion in acute heart failure.
- The implementation of a standardized natriuresis-guided protocol seems feasible and safe in a wide variety of health care settings.
- Several other trials on natriuresis-guided decongestion are ongoing and will provide data on longer term follow-up.

Nonstandard Abbreviations and Acronyms

ACEI	angiotensin converting enzyme inhibitor
ADVOR	Acetazolamide in Decompensated Heart Failure with Volume Overload
AHF	acute heart failure
ARB	angiotensin receptor blocker
ARNI	angiotensin receptor neprilysin inhibitor
DOSE-AHF	Determining Optimal Dose and Duration of Diuretic Treatment in People With Acute Heart Failure
ENACT-HF	Efficacy of a Standardized Diuretic Protocol in Acute Heart Failure
MRA	mineralocorticoid receptor antagonists
NT-proBNP	N-terminal pro-B-type natriuretic peptide
SGLT2i	sodium-glucose cotransporter-2 inhibitors

as a class I treatment to alleviate signs and symptoms of congestion, regardless of ejection fraction.[2,3] However, despite their ubiquitous use and guideline recommendation, data supporting diuretic strategies, including the type, dosage, and route of administration, are limited. Consequently, the Heart Failure Association of the European Society of Cardiology recently published a position article on the use of diuretics in AHF with volume overload.[4] This article recommends the prompt initiation of intravenous loop diuretics and early follow-up (within hours) of diuretic response, using either urine output or urinary sodium in a spot urine sample. The advantage of using urinary sodium is its convenience, as it does not require a 24-hour urine collection and allows for the rapid interpretation of the diuretic response. Furthermore, multiple studies have demonstrated that a low urinary sodium early after the first loop diuretics administration is associated with poor diuretic response and poor outcomes, irrespective of fluid loss.[5,6] The suggested flowchart, including the use of urinary sodium as a marker of diuretic response, has been adopted in the European Society of Cardiology guidelines on chronic and AHF.[2] In addition, a panel of American experts recently suggested a very similar protocol.[7] However, there are currently limited prospective data to support its use. Therefore, a multicenter, international study was conducted to assess the feasibility of a standardized diuretic protocol and its effect on diuretic response in various health care settings worldwide.

METHODS

The ENACT-HF study (Efficacy of a Standardized Diuretic Protocol in Acute Heart Failure) study was a nonrandomized, open-label, multicenter, pragmatic study conducted in 29 centers in 18 countries worldwide (Table S1; Figure S1). Its rationale and design have been published previously.[8] The study enrolled patients with AHF with (1) signs of volume overload, defined as either edema, ascites, and pleural effusion, (2) an NT-proBNP (N-terminal pro-B-type natriuretic peptide) >1000 pg/mL or a B-type natriuretic peptide level of >250 ng/mL, and (3) on a daily loop diuretic maintenance dose of at least 40 mg furosemide or equivalent (40 mg furosemide equals 1 mg bumetanide equals 20 mg torsemide) for at least 1 month. Patients were excluded if they had cardiogenic shock or systolic blood pressure <90 mm Hg, use of renal replacement therapy or ultrafiltration or use or anticipated use of intravenous inotropes. The study was designed as a 2-phase sequential study. During the first phase of the study, patients with AHF were treated according to the local institution's standard of care with the loop diuretic regimen left at the treating physician's discretion. In the second phase of the study, all centers implemented a standardized diuretic protocol. Centers transitioned to phase 2 when they had included 10 patients in phase 2 or alternatively when the aimed total number of patients in phase 1 was completely recruited. For practical reasons, recruitment was limited to working hours (8 AM–4 PM) to ensure good study conduct in all centers and to guarantee that the first urine collection would be at least 16 hours in duration. The study complied with the Declaration of Helsinki and was approved by the local ethics committees of the participating centers. The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Procedures

In the standard of care phase of the study, all doses, modes of administration (continuous infusion or bolus), and frequencies of loop diuretics were allowed at the discretion of the treating

physician. In addition, any combination of different types of diuretics could be used. In contrast, in the diuretic protocol phase of the study, diuretics were administered according to a predefined protocol based on the recent Heart Failure Association position article.[4] The backbone of the protocol were loop diuretic boluses that were administered intravenously twice daily (Figure S2). The first loop diuretic bolus was given at double the oral maintenance dose with an absolute maximum of 200 mg of furosemide equivalent dose. After 2 hours a spot urine sample was collected to measure urinary sodium. Diuretic response to the first loop diuretic bolus was assessed using urinary sodium (goal >50 mmol/L) and urine output (goal >100 mL/h). A second diuretic bolus was administered 6 to 12 hours after the first bolus. If both urinary sodium and urine output were above the predefined goal, the second bolus was administered at the same dose as the first dose. If either urinary sodium or urine output were below the predefined goal, escalation of the loop diuretic regimen was indicated. This escalation consisted of doubling of the loop diuretic dose to a maximum of 200 mg of furosemide equivalent dose or adding a thiazide if the maximum loop diuretic dose had already been reached. After 1 day of treatment, diuretic response was reevaluated by urine output. If the urine output was ≥3000 mL, the last diuretic administration was repeated twice daily. Otherwise, the diuretic regimen was escalated again and repeated twice daily.

In all patients, urine was collected for 2 consecutive days in 2 separate collections. Before any diuretic administration was given, the patient was asked to void empty. The first urine collection started when the first intravenous diuretic was given and continued until the next morning (8–10 AM) before the administration of new diuretics on the second day of the study. The second urine collection was started immediately after the first one and was continued for 24 hours. Both collections were sent to the local institution's lab to assess natriuresis. In addition, a spot urine sample was taken in all patients 2 hours after the first diuretic administration on the first day of the study to assess urinary sodium concentration.

End Points

The primary end point of the study was natriuresis after 1 day, defined as the total urinary sodium excretion from the moment the first diuretic was administered until the next morning (8–10 AM). Secondary end points were diuresis after 2 days, natriuresis after 2 days, weight loss after 2 days, change in Acetazolamide in Decompensated Heart Failure with Volume Overload (ADVOR) congestion score after 2 days, length of stay and in-hospital mortality. All investigators received training in the use of the ADVOR congestion score (Figure S3) before recruiting patients, which was a scoring system based on the presence of lower limb edema, pleural effusion and ascites (range 0–10 with higher numbers indicating more severe congestion).[9] The key safety end point was doubling of the serum creatinine compared with baseline at any time point during the study. Further, >50% decrease in estimated glomerular filtration rate, hypokalemia (serum potassium level of no >3 mmol/L) or hypotension (systolic blood pressure <90 mm Hg) at any time point were assessed as additional safety end points.

Statistical Analysis

Details on the power calculations have been published previously.[8] Based on a recent pilot trial in AHF,[10] the natriuresis after 1 day was estimated to be 234±133 mmol in the standard of care arm. An increase in natriuresis of 15% was deemed both achievable and clinically relevant. Assuming a 2-sided alpha of 0.05 and a statistical power of 80%, a sample size of 454 was calculated. To account for a potential withdrawal of or missing data in 10% of the patients, the final target sample was set at 500 patients. Due to funding constraints, recruitment was planned to conclude no later than December 2022. All patients with an available primary end point were included in the analysis of the primary and secondary end points according to their assigned treatment arms, irrespective of the correct performance of the diuretic protocol. Thirteen (3.2%) patients were excluded. No imputation of the primary end point was performed because of <5% of missing data. For the safety end points, all patients were analyzed according to the received intervention.

Baseline continuous variables are expressed as mean±SD if normally distributed or median (25th–75th percentile) otherwise and compared using a Student *t* test or Mann-Whitney *U* test as appropriate. Baseline categorical variables are expressed as number (%) and compared with a χ^2 test. All efficacy end points were investigated with a generalized linear mixed model with a random center effect and a fixed treatment arm effect. Differences in baseline characteristics between treatment arms with a $P<0.100$ were introduced as additional fixed effects. For the secondary end point of change in congestion score after 2 days, baseline congestion score was also introduced as a fixed effect. A logarithmic transformation was performed for the primary end point and for the secondary end points of natriuresis after 2 days, diuresis after 2 days and length of stay, because of skewed data and results are expressed as geometric mean (95% CI) with mean ratio (95% CI). Safety end points were compared using a Fisher exact test. The heterogeneity of the primary end point was tested in prespecified subgroups: (1) congestion score on admission ≥ versus < than the observed median, (2) estimated glomerular filtration rate ≥ versus < than the observed median, (3) chronic loop diuretic dose ≥ versus < than the observed median, (4) sex, and (5) left ventricular ejection fraction ≥50% versus <50%. Because potential variation in the duration of the urine collection could influence the primary end point, a sensitivity analysis after normalization of the primary end point for the duration of the urine collection was performed. All tests were 2-sided with a significance level set at $P<0.05$. All statistical analyses were performed with the use of SPSS for Windows, version 25 (IBM).

RESULTS

Between October 2019 and December 2022, 401 patients were enrolled of whom 254 in the standard of care arm and 147 in the protocol arm. Baseline characteristics are shown in Table 1 and were well balanced between both treatment arms. Patients were reflective of real life with mean age 70±14 years, median NT-proBNP 5888 (3200–11934) pg/mL, median estimated glomerular filtration rate of 49 (32–74) mL/min per 1.73 m^2, 55% of patients with a left ventricular ejection fraction <40% and a high comorbidity burden. Overall, baseline use of beta blockers was high, but there was

Table 1. Baseline Characteristics

	All (N=401)	Standard of care (N=254)	Protocol (N=147)	*P* value
Age, y	70±14	70±13	69±14	0.618
Sex (female)	151 (37.7%)	96 (37.8%)	55 (37.4%)	0.940
Ischemic cause	154 (38.4%)	89 (35.0%)	65 (44.2%)	0.069
Comorbidities				
Arterial hypertension	297 (74.1%)	192 (75.6%)	105 (71.4%)	0.359
Atrial fibrillation	230 (57.4%)	145 (57.1%)	85 (57.8%)	0.886
Diabetes	187 (46.6%)	110 (43.3%)	77 (52.4%)	0.079
Dyslipidemia	256 (63.8%)	157 (61.8%)	99 (67.3%)	0.266
Stroke	32 (8.0%)	21 (8.3%)	11 (7.5%)	0.780
Peripheral artery disease	44 (11.0%)	30 (11.8%)	14 (9.5%)	0.480
COPD	67 (16.7%)	44 (17.3%)	23 (15.6%)	0.665
Chronic kidney disease	201 (50.1%)	127 (50.0%)	74 (50.3%)	0.948
Weight, kg	82.7±21.5	83.2±22.8	81.6±19.1	0.468
Body mass index, kg/m²	29.5±6.6	29.7±7.1	29.2±5.5	0.400
Heart rate, bpm	83±20	83±20	82±22	0.834
Systolic blood pressure, mm Hg	126±22	127±23	124±21	0.283
Diastolic blood pressure, mm Hg	74±14	74±14	73±13	0.424
Congestion score	5 (3–6)	5 (4–7)	5 (3–6)	0.866
NT-proBNP, pg/mL	5888 (3200–11934)	5750 (3010–12685)	6137 (3266–11394)	0.761
LVEF mean (%)	39±15	40±16	37±14	0.107
LVEF categories				0.480
≤40%	223 (55.6%)	139 (54.7%)	84 (57.1%)	
41%–49%	61 (15.2%)	36 (14.2%)	25 (17.0%)	
≥50%	117 (29.2%)	79 (31.1%)	38 (25.9%)	
Hemoglobin, g/dL	12±2.3	12.2±2.3	12.2±2.5	0.965
Sodium, mmol/L	138±5	138±5	138±6	0.635
Potassium, mmol/L	4.3±0.6	4.2±0.6	4.3±0.7	0.732
Urea, mg/dL	56 (37–89)	55 (36–89)	58 (39–89)	0.426
Creatinine, mg/dL	1.3 (1.0–1.8)	1.3 (1.0–1.8)	1.3 (1.0–1.8)	0.836
eGFR, mL/min per 1.73 m²	49 (32–74)	50 (32–74)	48 (32–71)	0.993
Troponin, ng/L	40 (20–70)	40 (21–70)	40 (19–70)	0.122
Treatment				
Loop diuretic	401 (100%)	254 (100%)	147 (100%)	
Furosemide equivalent dose, mg	60 (40–90)	60 (40–80)	60 (40–100)	0.220
Thiazide	42 (10.5%)	24 (9.4%)	18 (12.2%)	0.378
Beta blocker	317 (79.1%)	195 (76.8%)	122 (83.0%)	0.140
ACEI/ARB/ARNI	270 (67.3%)	170 (66.9%)	100 (68.0%)	0.821
MRA	207 (51.6%)	120 (47.2%)	87 (59.2%)	0.021
SGLT2 inhibitor	68 (17.0%)	31 (12.2%)	37 (25.2%)	0.001
Ivabradine	19 (4.7%)	10 (3.9%)	9 (6.1%)	0.321
Digoxin	52 (13.0%)	34 (13.4%)	18 (12.2%)	0.743
CRT	34 (8.5%)	21 (8.3%)	13 (8.8%)	0.842
ICD	55 (13.7%)	33 (13.0%)	22 (15.0%)	0.580

ACEI indicates angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and SGLT2, sodium-glucose cotransporter 2.

a moderate use of ACEI (angiotensin converting enzyme inhibitor)/ARB (angiotensin receptor blockers)/ARNI (angiotensin receptor neprilysin inhibitor), and MRA (mineralocorticoid receptor antagonists). Few patients were receiving SGLT2i (sodium-glucose cotransporter-2 inhibitors).There was a higher use of MRA and SGLT2i in the protocol arm.

Primary End Point

The primary end point was missing in 9 (3.5%) patients in the standard of care arm and 4 (2.7%) patients in the protocol arm. The geometric mean of natriuresis after 1 day was 174 mmol (95% CI, 154–196) in the standard of care arm and 282 mmol (95% CI, 254–312) in the protocol arm (adjusted mean ratio, 1.64 [95% CI, 1.37–1.95]; *P*<0.001; Figure 1A; Table 2). Of note, the mean ratio was adjusted for baseline differences in diabetes, ischemic cause of heart failure, SGLT2i use, and MRA use. Unadjusted analyses rendered similar results and are provided in Table S2. The natriuresis was higher in the protocol arm compared with the standard of care arm across all prespecified subgroups (Figure 2; Table S3). Further, the difference was significantly higher in patients with lower estimated glomerular filtration rate and in patients with higher oral maintenance loop diuretics doses. The results were consistent when natriuresis was normalized for the duration of the urine collection in a sensitivity analysis (Table S4). Additionally, the higher natriuresis in the protocol arm was not modified by baseline use of MRA (*P* for interaction=0.774) or SGLT2i (*P* for interaction=0.417).

Secondary End Points

After 2 days of treatment, natriuresis was a geometric mean of 365 mmol (95% CI, 330–403) in the standard of care arm and 538 mmol (95% CI, 493–587) in the protocol arm (adjusted mean ratio, 1.52 [95% CI, 1.31–1.76]; *P*<0.001; Figure 1B; Table 2). The diuresis was a geometric mean of 4381 mL (95% CI, 4113–4667) in the standard of care arm and 5776 mL (95% CI, 5412–6162) in the protocol arm (adjusted mean ratio, 1.33 [95% CI, 1.21– 1.47]; *P*<0.001; Figure 1C; Table 2). There was no difference in weight loss or change in congestion score (Figure 3; Table 2). The length of stay was a geometric mean of 7.0 days (95% CI, 6.4–7.7) in the standard of care arm and 5.8 days (95% CI, 5.2–6.6) in the protocol arm (adjusted mean ratio, 0.87 [95% CI, 0.77–0.99]; Figure 4; Table 2). In-hospital mortality was low without a difference between both treatment arms (Table 2).

Safety End Points

All prespecified safety end points (hypokalemia, hypotension, worsening renal function) were comparable between both treatment arms (Table 3). In particular, doubling of serum creatinine occurred in 8 (3.1%) patients in the standard of care arm and 4 (2.7%) patients in the protocol arm (*P*=1.000).

Use of Diuretics

Details on the use of diuretics in both treatment arms are given in Table 4. The first loop diuretic dose

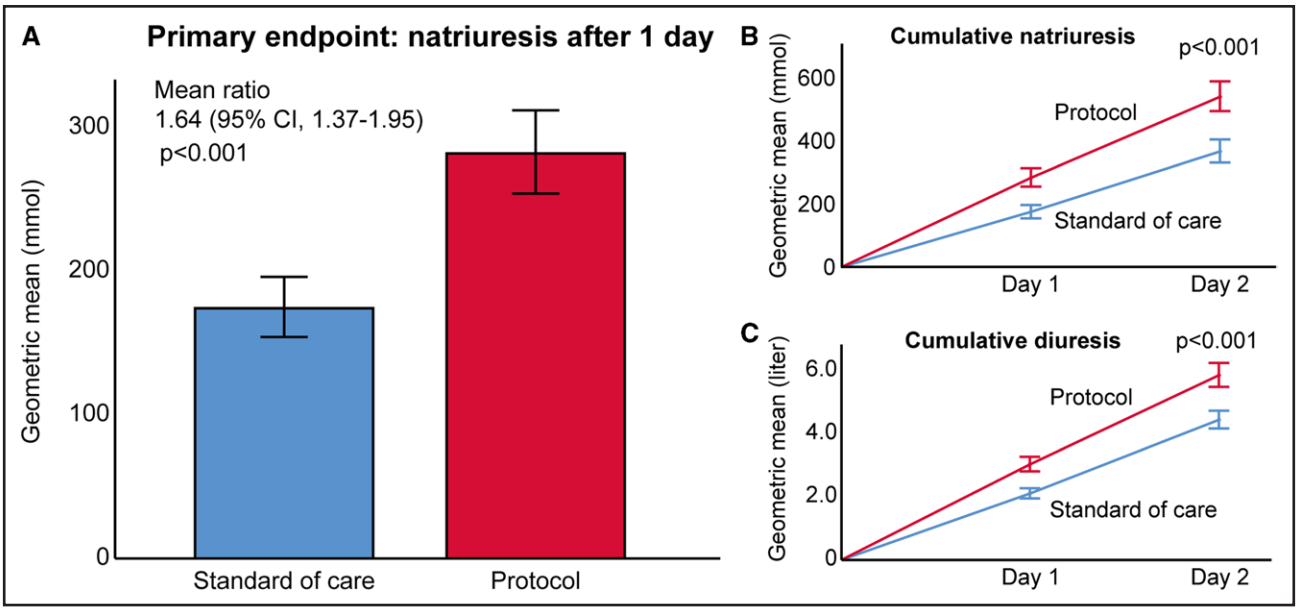

Figure 1. Natriuresis and diuresis.
A, Natriuresis after 1 day. **B**, Cumulative natriuresis after 2 days. **C**, Cumulative diuresis after 2 days. The error bars indicate the 95% CIs of the geometric mean. Mean ratios were adjusted for baseline differences. *P* values for cumulative natriuresis and cumulative diuresis indicate the significance of difference on day 2.

Table 2. Primary and Secondary End Points

	Standard of care (N=245)	Protocol (N=143)	Adjusted difference (95% CI)	*P* value
Primary end point				
Natriuresis after 1 day, mmol*	174 (154 to 196)	282 (254 to 312)	Mean ratio, 1.64 (1.37 to 1.95)	< 0.001
Secondary end points				
Natriuresis after 2 days, mmol*	365 (330 to 403)	538 (493 to 587)	Mean ratio, 1.52 (1.31 to 1.76)	< 0.001
Diuresis after 2 days, mL*	4381 (4113 to 4667)	5776 (5412 to 6162)	Mean ratio, 1.33 (1.21 to 1.47)	< 0.001
Weight loss after 2 days, kg	−3.4±2.7	−3.6±2.5	−0.2 (−0.8 to 0.3)	0.409
Change in congestion score after 2 days	−2.3±1.6	−2.5±1.7	−0.2 (−0.6 to 0.1)	0.180
Length of stay, d*	7.0 (6.4 to 7.7)	5.8 (5.2 to 6.6)	Mean ratio, 0.87 (0.77 to 0.99)	0.036
In-hospital mortality	5 (2.0%)	2 (1.4%)	Odds ratio, 0.90 (0.30 to 2.71)	0.847

All differences and *P* values were adjusted for baseline differences and calculated with a generalized linear mixed model with center as a random effect and treatment arm, baseline diabetes, ischemic cause of heart failure, baseline use of mineralocorticoid receptor antagonists, and baseline use of sodium-glucose cotransporter-2 inhibitor as fixed effects. For change in congestion score, the baseline congestion score was added as a fixed effect.

*Numbers represent geometric mean (95% CI).

administered was median 60 (40–80) mg of furosemide equivalent dose in the standard of care arm and 120 (80–160) mg in the protocol arm (*P*<0.001). The total cumulative loop diuretic dose across the 2 days was median 240 (195–391) mg of furosemide equivalent dose in the standard of care arm and 640 (320–760) mg in the protocol arm (*P*<0.001). Thiazides were used in in 14 (5.7%) patients in the standard of care arm and 27 (18.9%) patients in the protocol arm (*P*<0.001). The spot sodium sample was taken a median 2 (2–3) hours after the first loop diuretic administration. The number of patients with a urinary sodium concentration <50 mmol/L after 2 hours was 29 (11.8%) in the standard of care arm and 18 (12.6%) in the protocol arm (*P*=0.827), while the number of patients with a urine output <100 mL/h was 118 (48.2%) in the standard of care arm and 28 (19.6%) in the protocol arm (*P*<0.001). After 1 day of

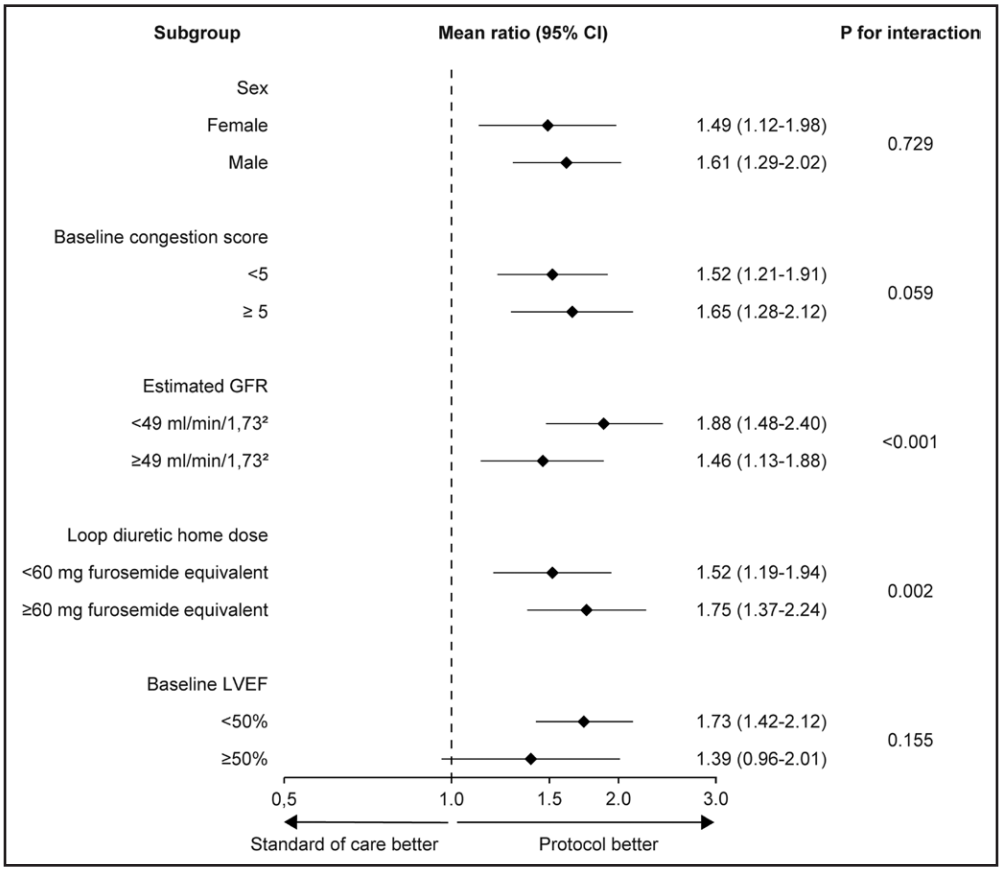

Figure 2. Subgroup analyses for the primary end point.
Mean ratios were adjusted for baseline differences. GFR indicates glomerular filtration rate; and LVEF, left ventricular ejection fraction.

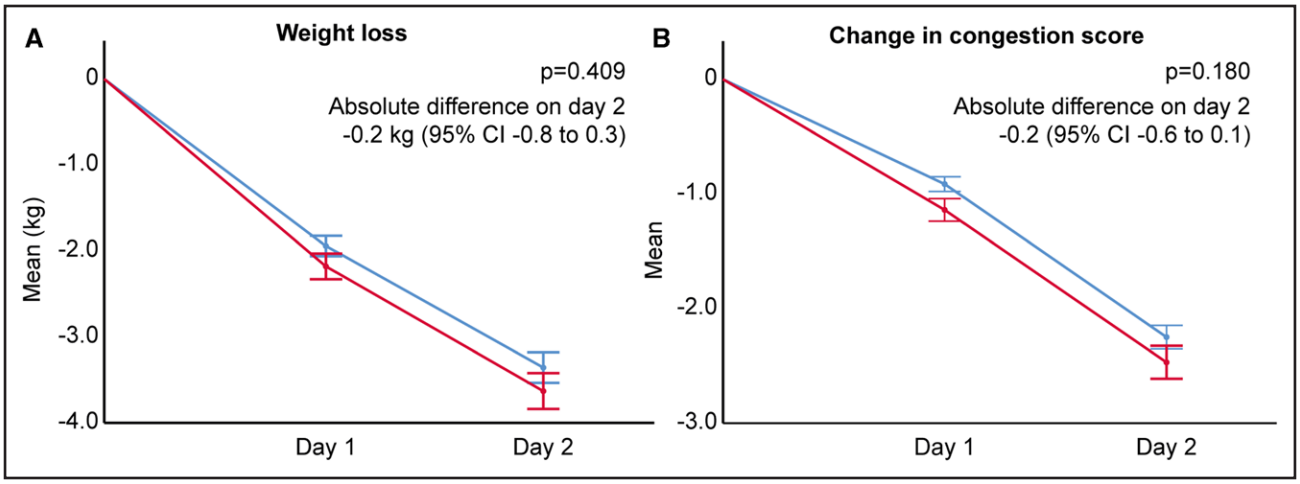

Figure 3. Weight loss and change in congestion score.
A, Weight loss. **B**, Change in congestion score. *P* values indicate the significance of difference on day 2. The error bars indicate SEs.

treatment, urine output was <3000 mL in 177 (72.2%) patients in the standard of care arm and 52 (36.4%) in the protocol arm. In the protocol arm, diuretic doses were changed in 50 (34.9%) patients with a total of 69 dose changes.

DISCUSSION

In this multicenter, international, pragmatic, open-label study of patients with AHF and volume overload, a standardized natriuresis-guided diuretic protocol, using spot urinary sodium and urine output to assess diuretic response early, was associated with an increased natriuresis compared with standard of care after 1 day. In addition, patients treated according to the protocol had higher natriuresis and diuresis after 2 days and a shorter length of stay without an increase in safety events.

The diuretic protocol of this study was based on the recent Heart Failure Association position article and current European guidelines[2,4] and was for the first time shown not only to be feasible, but also to effectively increase natriuresis in different health care settings. Indeed, the ENACT-HF study recruited patients from 4 different continents and demonstrated a highly significant increase in natriuresis and diuresis after implementation of the diuretic protocol. Natriuresis is a very relevant end point because it is one of the most direct measurements of diuretic response,[11] and poor natriuresis has been associated with worse outcomes.[6]

Importantly, the protocol was advantageous across all subgroups, but there was even a greater benefit in patients with lower estimated glomerular filtration rate and patients on higher oral maintenance loop diuretic doses. As these 2 latter groups represent patients who inherently exhibit higher diuretic resistance,[7] a tailored diuretic protocol may aid even more in improving diuretic response.

The diuretic protocol led to the use of higher doses of loop diuretics and more frequent combinational therapy with thiazides. Of note, the first loop diuretic dose was similar to the oral maintenance dose when left at the treating physician's discretion in the standard of care arm, while the protocol mandated to start with the double of the oral maintenance dose. In the DOSE-AHF

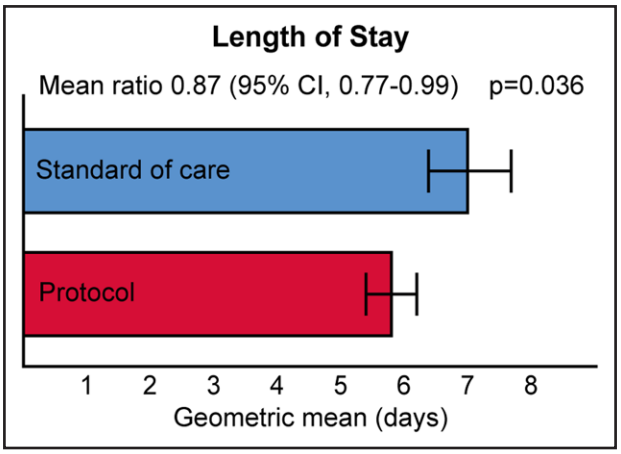

Figure 4. Length of stay.
Mean ratios were adjusted for baseline differences.

Table 3. Safety End Points

	Standard of care (N=254)	Protocol (N=147)	*P* value
Renal			
Doubling creatinine from baseline	8 (3.1%)	4 (2.7%)	1.000
eGFR decrease ≥50%	10 (3.9%)	5 (3.4%)	1.000
Hypokalemia	30 (11.8%)	18 (12.2%)	0.875
Hypotension	12 (4.7%)	7 (4.8%)	1.000

Hypokalemia was defined as a serum potassium ≤3 mmol/L at any time during study treatment. Hypotension was defined as systolic blood pressure <90 mm Hg at any time during study treatment. eGFR indicates estimated glomerular filtration rate.

Table 4. Use of Diuretics During the 2-Day Study Period

	Standard of care (N=245)	Protocol, (N=143)	*P* value
Chronic oral maintenance dose as furosemide equivalent dose, mg	60 (40–80)	60 (40–100)	0.220
Loop diuretic use			
First loop diuretic dose as furosemide equivalent dose, mg	60 (40–80)	120 (80–200)	<0.001
Cumulative furosemide equivalent dose, mg	240 (195–391)	640 (320–760)	<0.001
Use of continuous infusion	60 (24.5%)	0	<0.001
Use of bolus	229 (93.5%)	143 (100%)	0.002
Number of loop diuretic doses			<0.001
2 doses	33 (13.5%)	3 (2.1%)	
3 doses	55 (22.4%)	8 (5.6%)	
4 doses	50 (20.4%)	126 (88.1%)	
≥5 doses	107 (43.7%)	6 (4.2%)	
Use of thiazides	14 (5.7%)	27 (18.9%)	<0.001
Use of acetazolamide	4 (1.6%)	1 (0.7%)	0.656
Diuretic response assessment after first diuretic bolus			
Spot urinary sodium after 2 hour			
Mean, mmol/L	93±33	94±32	0.801
<50 mmol/L	29 (11.8%)	18 (12.6%)	0.827
Urine output			
Median, mL/h	102 (70–150)	144 (117–194)	<0.001
<100 mL/h	118 (48.2%)	28 (19.6%)	<0.001
Diuretic response assessment after 1 day of treatment			
Total urine output day 1			
Median, mL	2200 (1450–3127)	3126 (2300–4000)	<0.001
<3000 mL	177 (72.2%)	52 (36.4%)	<0.001

trial (Determining Optimal Dose and Duration of Diuretic Treatment in People With Acute Heart Failure) trial, 2.5× the oral maintenance dose twice daily was not associated with an improvement in patients' global assessment of symptoms in comparison with 1× the oral maintenance dose, but increased net fluid loss and weight loss after 72 hours. The current European Society of Cardiology guidelines leave it open whether the starting loop diuretic dose should be equal to or the double of the oral maintenance dose,[2] but the results of the current study, as well as the ADVOR trial[9] and the DOSE-AHF trial[12] suggest that starting with double of the oral maintenance dose may be preferable. Despite the use of higher loop diuretic doses in the protocol arm, this was not associated with an increase in safety events. Furthermore, in-hospital mortality was low and not significantly different between the protocol arm and the standard of care arm.

Although the diuretic protocol was associated with an increased natriuresis and diuresis, there was no increase in the secondary end-points of weight loss or a higher decrease in the congestion score after 2 days. While weight loss has been associated with improved outcomes,[13,14] it might be subject to greater measurements errors in the pragmatic design of this study,[15] which was also a reason not to use it as the primary end point. Analysis of weight dynamics preceding hospitalization has demonstrated to be a sensitive tool in determining the amount of volume overload. This is based on the premise that a baseline dry weight has been established, taking into consideration weight changes are limited that on an individual basis.[16] In addition, correlations between fluid and weight loss during treatment of AHF are at best,[17] possibly explained by the fact that daily weights can be challenging to obtain accurately (ie, not weighing patients on the same scale, weighing different times in the day and in relation to meals/urination/defecation, use of bed scales, and different clothing or devices like telemetry).[15] Further, a difference between arms might have become apparent only after a longer treatment period.

Congestion was graded with the ADVOR congestion score. This score was used to assess the primary end point of effective decongestion in the ADVOR trial, showing an increase in decongestion when loop diuretics were combined with acetazolamide in patients with AHF and volume overload. As the ADVOR congestion score quantifies edema, pleural effusion and ascites (the latter 2 via technical exams), it might be less sensitive to detect differences in congestion only after 2 days of treatment in the current study population. Furthermore, the patients in the current study had a higher congestion score than those in the ADVOR trial[9] and only small decreases in their score in both arms, which might imply that a longer treatment

period might be necessary to show any difference. Moreover, pleural effusion and ascites were not screened in all patients, but only needed confirmation with imaging in case of clinical suspicion, which might limit the sensitivity of the congestion assessment. Of note, the length of stay was shortened by 1 day in the protocol arm, which might suggest more effective decongestion.

The ENACT-HF study is the first in a series of trials on natriuresis-guided decongestion. More data are to be expected from PUSH-AHF (Pragmatic Urinary Sodium-Based Algorithm in Acute Heart Failure; NCT04606927),[18] ESCALATE (Urine Chemistry Guided Acute Heart Failure Treatment; NCT04481919), and DECONGEST (Diuretic Treatment in Acute Heart Failure With Volume Overload Guided by Serial Spot Urine Sodium Assessment; NCT05411991).

The ENACT-HF study is subject to certain limitations. First, the study has a nonrandomized, open-label design which makes it subject to bias by the investigators. However, the sequential nature of the study ensured that centers had to recruit patients in the standard of care arm first (where any dose change was left at the discretion of the treating physician) before proceeding to treating patients according to the protocol (where the dosing was protocolized). As such, they had no opportunity to compare the results of their standard of care with the protocol. In addition, randomization within centers would have had the disadvantage of centers learning from a potentially beneficial protocol and changing their routine treatment plan, while still including patients in the standard of care arm (contamination). Second, the sequential design of the study implies changes in heart failure care over time might influence the study results. Third, recruitment was not completed as intended (n=500) due to lack of funding. Despite the lower than intended recruitment, there was a very clear and highly significant difference in the primary end point. This difference was much higher than anticipated when performing the power calculations. Therefore, a lower sample size would probably have sufficed. Fourth, safety end points were only collected for the first 2 days and for that reason, safety cannot be guaranteed beyond this period. In addition, only rudimentary assessment of safety end points was done without adjudication. Last, the statistical methods used to adjust for baseline characteristics imbalances might be insufficient to account for residual confounders.

CONCLUSIONS

The use of a standardized natriuresis-guided loop diuretic protocol was feasible, safe, and associated with an increased natriuresis and diuresis and a shorter length of stay.

ARTICLE INFORMATION

Received August 2, 2023; accepted October 25, 2023.

Affiliations

Ziekenhuis Oost-Limburg, Department of Cardiology, Genk, Belgium (J.D., P.N., M.D., P.M.). UHasselt, Doctoral School for Medicine and Life Sciences, LCRC, Diepenbeek, Belgium (J.D., W.M.). Department of Cardiology, Sonography and Functional Diagnostics, First Moscow State Medical University, Russia (K.C.). Department of Noninvasive Cardiology, Medical University of Lodz, Poland (M.L.). Department of Cardiology, Heart Failure and Heart Transplant Unit, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain (I.Z.-R.). Department of Cardiology, Mount Lebanon Hospital-Balamand University Medical Center, Hazmiyeh (S.N.). Instituto Nacional de Cardiología Ignacio Chávez, Ciudad de México (C.P.P.-P.). Department of Cardiology, Faculty of Medicine, University of Debrecen, Hungary (A.B.). Department of Cardiology, Thorax Centrum Twente, Medisch Spectrum Twente, Enschede, the Netherlands (F.E.). Benyoucef Benkhedda Faculty of Medicine, Mustapha Pacha Hospital, University of Algiers, Algeria (R.B.). Department of Cardiology, Hospital Universitario Puerta de Hierro Majadahonda (IDIPHISA), Madrid, Spain; Centro de Investigación Biomédica en Red en Enfermedades Cardiovasculares (CIBERCV), Madrid, Spain (M.C.-M.). Advanced Heart Failure and Heart Transplant Unit, Department of Cardiology, Complexo Hospitalario Universitario A Coruña (CHUAC), Servicio Galego de Saúde (SERGAS), A Coruña, Spain; Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Instituto de Salud Carlos III, Madrid, Spain (G.B.-C.). Pushpagiri Institute of Medical Sciences, Tiruvalla, India (V.G.). Theracardia, Brasov, Romania (C.Z.). Kuala Lumpur General Hospital, Malaysia (N.T.R.). University Hospitals of North Midlands, Stoke on Trent, United Kingdom (D.B.). Wetchakarunrasm Hospital, Bangkok, Thailand (A.L.). Division of Cardiology, Città della Salute e della Scienza University Hospital of Torino, Turin, Italy (S.F.). National Heart Institute, Kuala Lumpur, Malaysia (A.M.G.). Department of Cardiology, University Heart and Vascular Center Hamburg, Germany (D.K.). Department of Cardiology, CHU Ibn Sina, Mohammed V University, Rabat, Morocco (N.D.). Zan Mitrev Clinic, Skopje, North Macedonia (M.K.). Department of Cardiology, Hospital Professor Doutor Fernando Fonseca, Amadora, Portugal (I.F.). Department of Cardiology, Michele e Pietro Ferrero Hospital, Verduno, Italy (V.B.). Department of Internal Medicine, Red Cross Hospital, Bremen, Germany (H.F.). Jordan Hospital, Amman, Jordan (I.A.A.). Ospedale Sant'Andrea, Vercelli, Italy (A.G.). Cardiology Department, Hospital Clínico Universitario de Valencia, Spain (R.d.l.E.). Department of Cardiology, Abdali Hospital, Amman, Jordan (R.T.). Emergency Department, Hospital Clínic de Barcelona, IDIBAPS, University of Barcelona, Catalonia, Spain (Ò.M.). The Heart Centre, Royal Infirmary of Edinburgh, United Kingdom (J.S.S.). UHasselt, Biomedical Research Institute, Faculty of Medicine and Life Sciences, LCRC, Diepenbeek, Belgium (W.M.).

Sources of Funding

Drs Dauw and Mullens are researchers for the Limburg Clinical Research Center UHasselt-ZOL-Jessa, supported by the foundation Limburg Sterk Merk, province of Limburg, Flemish government, Hasselt University, Ziekenhuis Oost-Limburg, and Jessa Hospital.

Disclosures

Dr Dauw received speaker fees from AstraZeneca, Boehringer-Ingelheim, and Bayer; Dr Lelonek received speaker and consulting fees from Novartis, Novo Nordisk, Servier, AstraZeneca, Boehringer-Ingelheim, Bausch Health, Bayer, Ewopharma, and Gedeon Richter and was involved in clinical trials from Amgen, Novartis, Novo Nordisk, and Boehringer-Ingelheim; Dr Borbély received speaker fees from Astra Zeneca, Bayer, Boehringer-Ingelheim, and Novartis; Dr Cobo-Marcos received speaker fees from Astra Zeneca, Boehringer-Ingelheim, Novartis, Vifor Pharma, Novo Nordisk, and Bayer; Dr Barge-Caballero received travel grants and speaker fees from Astra Zeneca, Boehringer-Ingelheim, Novartis, Viatris, and Pfizer and received research grants from Pfizer; Dr Barker received speaker fees from AstraZeneca, Novartis, and Medtronic; Dr Doghmi received speaker fees from Novartis, Boehringer-Ingelheim, and Pfizer; Dr Nijst received speaker fees from Novartis, Boehringer-Ingelheim, and Bayer; and Dr Martens received consultancy fees from Novartis and CLS Vifor and is supported by a research grant from the Belgian American Educational Foundation and the Frans Van de Werf Fund. The other authors report no conflicts.

Supplemental Material

Tables S1–S4
Figures S1–S3

REFERENCES

1. Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Follath F, Harjola VP, Hochadel M, Komajda M, Lassus J, Lopez-Sendon JL, et al. EuroHeart Failure Survey II

(EHFS II): a survey on hospitalized acute heart failure patients: description of population. *Eur Heart J.* 2006;27:2725–2736. doi: 10.1093/eurheartj/ehl193
2. McDonagh TA, Metra M, Adamo M, Baumbach A, Böhm M, Burri H, Čelutkiene J, Chioncel O, Cleland JGF, Coats AJS, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J.* 2021;42:3599–3726. doi: 10.1093/eurheartj/ehab368
3. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, Deswal A, Drazner MH, Dunlay SM, Evers LR, et al. 2022 AHA/ACC/HFSA Guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation.* 2022;145:e895–e1032. doi: 10.1161/CIR.0000000000001063
4. Mullens W, Damman K, Harjola VP, Mebazaa A, Brunner-La Rocca HP, Martens P, Testani JM, Tang WHW, Orso F, Rossignol P, et al. The use of diuretics in heart failure with congestion — a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail.* 2019;21:137–155. doi: 10.1002/ejhf.1369
5. Hodson DZ, Griffin M, Mahoney D, Raghavendra P, Ahmad T, Turner J, Wilson FP, Tang WHW, Rao VS, Collins SP, et al. Natriuretic response is highly variable and associated with 6-month survival: insights from the ROSE-AHF trial. *JACC. Heart Fail.* 2019;7:383–391. doi: 10.1016/j.jchf.2019.01.007
6. Tersalvi G, Dauw J, Gasperetti A, Winterton D, Cioffi GM, Scopigni F, Pedrazzini G, Mullens W. The value of urinary sodium assessment in acute heart failure. *Eur J Heart Fail.* 2021;10:216–223. doi: 10.1093/ehjacc/zuaa006
7. Felker GM, Ellison DH, Mullens W, Cox ZL, Testani JM. Diuretic therapy for patients with heart failure: JACC state-of-the-art review. *J Am Coll Cardiol.* 2020;75:1178–1195. doi: 10.1016/j.jacc.2019.12.059
8. Dauw J, Lelonek M, Zegri-Reiriz I, Paredes-Paucar CP, Zara C, George V, Cobo-Marcos M, Knappe D, Shchekochikhin D, Lekhakul A, et al. Rationale and design of the efficacy of a standardized diuretic protocol in acute heart failure study. *ESC Heart Fail.* 2021;8:4685–4692. doi: 10.1002/ehf2.13666
9. Mullens W, Dauw J, Martens P, Verbrugge FH, Nijst P, Meekers E, Tartaglia K, Chenot F, Moubayed S, Dierckx R, et al; ADVOR Study Group. Acetazolamide in acute decompensated heart failure with volume overload. *N Engl J Med.* 2022;387:1185–1195. doi: 10.1056/NEJMoa2203094
10. Verbrugge FH, Martens P, Ameloot K, Haemels V, Penders J, Dupont M, Tang WHW, Droogné W, Mullens W. Acetazolamide to increase natriuresis in congestive heart failure at high risk for diuretic resistance. *Eur J Heart Fail.* 2019;21:1415–1422. doi: 10.1002/ejhf.1478
11. Verbrugge FH. Editor's Choice-Diuretic resistance in acute heart failure. *Eur Heart J Acute Cardiovasc Care.* 2018;7:379–389. doi: 10.1177/2048872618768488
12. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, LeWinter MM, Deswal A, Rouleau JL, Ofili EO, et al; NHLBI Heart Failure Clinical Research Network. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med.* 2011;364:797–805. doi: 10.1056/NEJMoa1005419
13. Valente MAE, Voors AA, Damman K, Van Veldhuisen DJ, Massie BM, O'Connor CM, Metra M, Ponikowski P, Teerlink JR, Cotter G, et al. Diuretic response in acute heart failure: clinical characteristics and prognostic significance. *Eur Heart J.* 2014;35:1284–1293. doi: 10.1093/eurheartj/ehu065
14. Gill GS, Lam PH, Brar V, Patel S, Arundel C, Deedwania P, Faselis C, Allman RM, Zhang S, Morgan CJ, et al. In-hospital weight loss and outcomes in patients with heart failure. *J Card Fail.* 2022;28:1116–1124. doi: 10.1016/j.cardfail.2021.11.017
15. Nohria A, Drazner MH. Should weight loss be targeted during an acute heart failure admission? *J Card Fail.* 2022;28:1125–1127. doi: 10.1016/j.cardfail.2022.01.014
16. Chaudhry SI, Wang Y, Concato J, Gill TM, Krumholz HM. Patterns of weight change preceding hospitalization for heart failure. *Circulation.* 2007;116:1549–1554. doi: 10.1161/circulationaha.107.690768
17. Testani JM, Brisco MA, Kociol RD, Jacoby D, Bellumkonda L, Parikh CR, Coca SG, Tang WHW. Substantial discrepancy between fluid and weight loss during acute decompensated heart failure treatment. *Am J Med.* 2015;128:776–83.e4. doi: 10.1016/j.amjmed.2014.12.020
18. ter Maaten JM, Beldhuis IE, van der Meer P, Krikken JA, Coster JE, Nieuwland W, van Veldhuisen DJ, Voors AA, Damman K. Natriuresis-guided therapy in acute heart failure: rationale and design of the Pragmatic Urinary Sodium-based treatment algoritHm in Acute Heart Failure (PUSH-AHF) trial. *Eur J Heart Fail.* 2022;24:385–392. doi: 10.1002/ejhf.2385