ESC HEART FAILURE
ESC Heart Failure 2024; **11**: 1767–1776
Published online 21 February 2024 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.14720

STUDY DESIGN

Design and baseline characteristics of SALT-HF trial: hypertonic saline therapy in ambulatory heart failure

M. Cobo Marcos[1,2], J. Comín-Colet[2,3], R. de la Espriella[4], J. Rubio Gracia[5], J. L. Morales-Rull[6,7], I. Zegrí[8], P. Llacer[9,10], P. Diez-Villanueva[11], S. Jiménez-Marrero[3], J. de Juan Bagudá[2,12,13,14], C. Ortiz Cortés[15], J. Goirigolzarri-Artaza[16], J. M. García-Pinilla[17,18,19], E. Barrios[20], S. del Prado Díaz[2,21], E. Montero Hernández[22], M. Sanchez-Marteles[5] and J. Nuñez[2,4]*

[1]*Department of Cardiology, Hospital Universitario Puerta de Hierro, Madrid, Spain;* [2]*Centro de Investigación Biomédica en Red (CIBER Cardiovascular), Madrid, Spain;* [3]*Department of Cardiology, Hospital Universitario de Bellvitge, IDIBELL, Barcelona, Spain;* [4]*Department of Cardiology, Hospital Clínico Universitario de Valencia (INCLIVA), University of Valencia, Valencia, Spain;* [5]*Department of Internal Medicine, Hospital Universitario Lozano Blesa, University of Zaragoza, Aragon Health Research Institute (IIS Aragon), Zaragoza, Spain;* [6]*Department of Internal Medicine, Hospital Universitario Arnau de Vilanova, Lleida, Spain;* [7]*Heart Failure Unit, Lleida Health Region, Institut de Recerca Biomèdica de Lleida (IRBLleida), Lleida, Spain;* [8]*Department of Cardiology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain;* [9]*Department of Internal Medicine, Hospital Universitario Ramón y Cajal, IRYCIS, Madrid, Spain;* [10]*Department of Medicine and Medical Specialties, Facultad de Medicina y Ciencias de la Salud, Universidad de Alcalá, Madrid, Spain;* [11]*Department of Cardiology, Hospital Universitario de la Princesa, Madrid, Spain;* [12]*Department of Cardiology, University Hospital 12 de Octubre, Instituto de Investigación Sanitaria Hospital 12 de Octubre (imas12), Madrid, Spain;* [13]*Instituto de Salud Carlos III, Madrid, Spain;* [14]*Department of Medicine, Faculty of Biomedical and Health Science, Universidad Europea de Madrid, Madrid, Spain;* [15]*Department of Cardiology, Hospital Universitario San Pedro de Alcántara, Cáceres, Spain;* [16]*Department of Cardiology, Hospital Universitario Clínico San Carlos, Madrid, Spain;* [17]*Department of Cardiology, Hospital Universitario Virgen de la Victoria, Málaga, Spain;* [18]*Instituto de Investigación Biomédica-Plataforma BIONAND. Málaga Ciber-Cardiovascular, Málaga, Spain;* [19]*Insitituto de Salud Carlos III. Departamento de Medicina y Dermatología, Universidad de Málaga, Málaga, Spain;* [20]*Department of Cardiology, Hospital Universitario Rey Juan Carlos Móstoles, Madrid, Spain;* [21]*Department of Cardiology, Hospital Universitario Ramón y Cajal, Madrid, Spain; and* [22]*Department of Internal Medicine, Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain*

Abstract

Aims Hypertonic saline solution (HSS) plus intravenous (IV) loop diuretic appears to enhance the diuretic response in patients hospitalized for heart failure (HF). The efficacy and safety of this therapy in the ambulatory setting have not been evaluated. We aimed to describe the design and baseline characteristics of the SALT-HF trial participants.

Methods and results 'Efficacy of Saline Hypertonic Therapy in Ambulatory Patients with HF' (SALT-HF) trial was a multicenter, double-blinded, and randomized study involving ambulatory patients who experienced worsening heart failure (WHF) without criteria for hospitalization. Enrolled patients had to present at least two signs of volume overload, use $\geq$ 80 mg of oral furosemide daily, and have elevated natriuretic peptides. Patients were randomized 1:1 to treatment with a 1-h infusion of IV furosemide plus HSS (2.6–3.4% NaCl depending on plasmatic sodium levels) versus a 1-h infusion of IV furosemide at the same dose (125–250 mg, depending on basal loop diuretic dose). Clinical, laboratory, and imaging parameters were collected at baseline and after 7 days, and a telephone visit was planned after 30 days. The primary endpoint was 3-h diuresis after treatment started. Secondary endpoints included (a) 7-day changes in congestion data, (b) 7-day changes in kidney function and electrolytes, (c) 30-day clinical events (need of IV diuretic, HF hospitalization, cardiovascular mortality, all-cause mortality or HF-hospitalization).

Results A total of 167 participants [median age, 81 years; interquartile range (IQR), 73–87, 30.5% females] were randomized across 13 sites between December 2020 and March 2023. Half of the participants (n = 82) had an ejection fraction >50%. Most patients showed a high burden of comorbidities, with a median Charlson index of 3 (IQR: 2–4). Common co-morbidities included diabetes mellitus (41%, n = 69), atrial fibrillation (80%, n = 134), and chronic kidney disease (64%, n = 107).
Patients exhibited a poor functional NYHA class (69% presenting NYHA III) and several signs of congestion. The mean composite congestion score was 4.3 (standard deviation: 1.7). Ninety per cent of the patients (n = 151) presented oedema and jugular engorgement, and 71% (n = 118) showed lung B lines assessed by ultrasound. Median inferior vena cava diameter was 23 mm, (IQR: 21–25), and plasmatic levels of N-terminal-pro-B-type natriuretic peptide (NTproBNP) and antigen carbohydrate 125 (CA125) were increased (median NT-proBNP 4969 pg/mL, IQR: 2508–9328; median CA125 46 U/L, IQR: 20–114).

Conclusions SALT-HF trial randomized 167 ambulatory patients with WHF and will determine whether an infusion of hypertonic saline therapy plus furosemide increases diuresis and improves decongestion compared to equivalent furosemide administration alone.

Keywords Diuretic resistance; Hypertonic saline solution; Hypertonic therapy; Outpatient with heart failure

Received: 9 November 2023; Revised: 22 January 2024; Accepted: 29 January 2024
**Correspondence to:*
Julio Núñez, Department of Cardiology, Hospital Clínico Universitario de Valencia, Department of Medicine, Universitat de Valencia, Avda. Blasco Ibáñez 17, 46010 Valencia, Spain.
Email: yulnunez@gmail.com; juenuvi@uv.es

Introduction

The traditional model of managing worsening heart failure (WHF) in both inpatient and outpatient settings has several inherent challenges. Although essential for patients exhibiting severe symptoms such as respiratory failure and unstable arrhythmia, hospitalization is not always needed in patients in whom volume overload is the main driver of worsening symptoms.[1] In fact, the reliance on hospitalization is sometimes primarily due to the convenience of administering IV diuretic therapy and conducting close clinical and laboratory monitoring, highlighting a gap in outpatient care options for WHF patients.[2] This underscores the need to explore alternative, potentially more efficient, outpatient treatment modalities for managing WHF effectively.

Recognizing that diuresis is the primary intervention in patients hospitalized for HF decompensations and that some patients quickly improve with therapy (i.e. within hours), HF clinics have emerged as outpatient models aiming to provide comprehensive care where patients may obtain same-day or walk-in visits for worsening symptoms rather than a potential visit to the emergency department.[3,4] However, although some diuretic protocols have been proposed,[1,2,5] no randomized trials have evaluated different diuretic strategies in the outpatient setting.

Observational and randomized trials have evaluated IV furosemide and hypertonic saline solution (HSS) in hospitalized patients with acute HF. This therapy has been associated with increased diuretic efficiency, fluid and weight loss, and a decreased incidence of HF rehospitalizations.[6–10]

However, the efficacy and safety of this approach in the ambulatory setting have not been evaluated. This study aims to bridge this gap by assessing both efficacy and safety, as well as feasibility, of this combined therapy (HSS plus IV furosemide) in ambulatory patients with WHF and systemic fluid overload.

Study design

The SALT-HF trial was a multicenter, double-blinded, and randomized trial involving ambulatory patients who presented an episode of WHF that required IV diuretics and without criteria for hospital admission at the treating physician's discretion. Patients were randomized to treatment with a 60-min infusion of IV furosemide (125–250 mg) plus HSS (intervention group) versus an infusion of IV furosemide (125–250 mg) without HSS (control group), as is shown in *Figure 1*.

The research team conducted training sessions on the design and implementation of the protocol before and during the start of the study.

The local institutional ethics committees approved the trial, and it was conducted in accordance with the Declaration of Helsinki and the International Conference of Harmonization Guidelines for Good Clinical Practice. All participants provided written informed consent. The trial was registered at ClinicalTrials.gov (NCT04533997).

Eligibility

The study's inclusion and exclusion criteria are listed in *Table 1*. Patients were eligible if they presented with WHF and at least two signs of volume overload (peripheral oedema, jugular enlargement, ascites, or pleural effusion) and had an N-terminal pro-B-type natriuretic peptide (NT-proBNP) $>$ 1000 pg/mL or a B-type natriuretic peptide (BNP) $>$ 250 ng/mL. In addition, patients should be treated with oral loop diuretics for $\geq$1 month before inclusion at a dose of $\geq$80 mg of furosemide or $\geq$40 mg of torsemide per day. The diagnosis of HF was assessed by the treating physician based on the current HF guidelines.[11–13] Key exclusion criteria included any of the following: cardiogenic shock, renal replacement therapy, severe metabolic derangements, or other high-risk criteria that would require hospitalization.

The study did not include individuals with acute pulmonary oedema or basal oxygen saturation below 90%.

Objectives and endpoints

The primary objective of the SALT-HF trial was to test whether the administration of HSS plus IV furosemide can improve decongestion over IV furosemide in WHF outpatients

Figure 1 SALT-HF trial design.

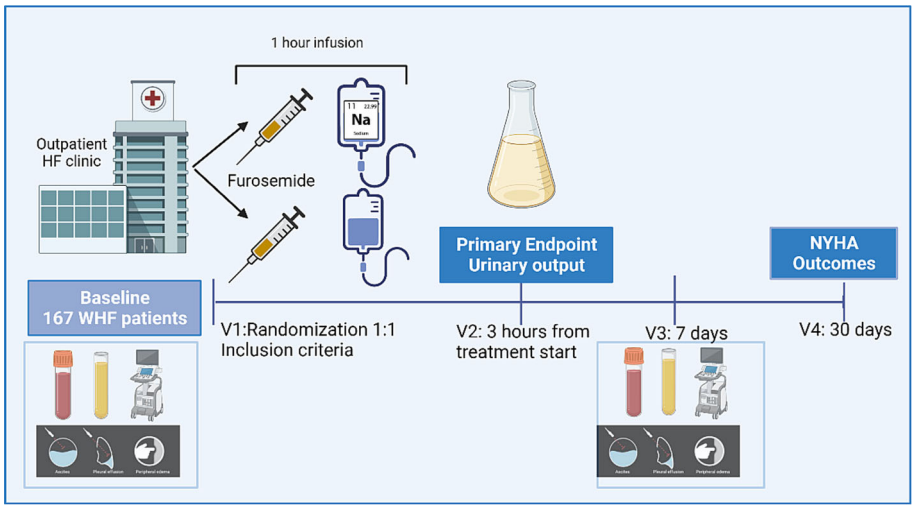


Table 1 Eligibility criteria of SALT-HF trial

Inclusion criteria

- A clinical diagnosis of acute heart failure and at least two signs of volume overload:
  - Pitting oedema
  - Jugular enlargement
  - Ascites
  - Pleural effusion
- Maintenance of daily oral loop diuretic use of ≥80 mg furosemide or ≥40 mg torsemide for ≥1 month.
- BNP > 250 ng/ml or NT-proBNP >1000 pg/mL at time of screening.
- Stable treatment in the previous 2 weeks (except diuretic).
- Need for intravenous diuretic therapy to relieve congestion, according to the responsible physician.

Exclusion criteria

- Cardiogenic shock or systolic blood pressure <90 mmHg or >180 mmHg.
- Hospital admission criteria in the opinion of the treating physician.
- Acute Pulmonary oedema or basal oxygen saturation less than 90%.
- Clinically significant arrhythmia or heart rate >150 b.p.m. or <40 b.p.m.
- Patients in haemodialysis or peritoneal dialysis programme.
- Serum sodium <125 mEq/L or > 145 mEq/L.
- Serum potassium <3.5 mEq/L.
- Haemoglobin <9 g/dL
- Acute coronary syndrome or cardiological procedure in the previous 4 weeks.
- Severe uncorrected valve disease except tricuspid regurgitation.
- Moderate or severe dementia, active delirium, or psychiatric problems.
- Patients in whom cardiac surgery or device implantation is planned in the following 30 days.
- Pregnancy or breastfeeding.
- Inability to give informed consent in the absence of a legal officer.
- Inability to collect the urine.
- Patients on tolvaptan.

NT-proBNP, N-terminal pro-B-type natriuretic peptide.

with predominant systemic volume overload. The hypothesis was that the combination therapy increases the diuresis volume 3 h after the start of treatment.

Primary endpoint

Diuresis after 3 h of treatment start was selected as the primary endpoint.

Secondary endpoints

Secondary endpoints included between-treatment changes in (a) urinary sodium and body weight 3 h after treatment, (b) 7-day changes in congestion parameters that included the composite congestion score, the body weight, the diameter of inferior vena cava, the presence of lung B-lines by ultrasound, haemoconcentration parameters (haematocrit, albumin and proteins), and circulating biomarkers such as NT-proBNP, antigen carbohydrate 125 (CA125), and urinary sodium, (c) 7-day changes in NYHA and visual analogue scale (*Table 2*).

The decision to evaluate secondary clinical endpoints at 7 days was made to provide a pragmatic approach in line with routine clinical practice.

Safety endpoints

The safety endpoints included (a) 7-day worsening of kidney function defined as an increase in serum creatinine ≥0.3 mg/dL, (b) electrolyte abnormalities defined as hypokalaemia (K^+ < 3.5 mEq/L) or hyperkalaemia (K^+ > 5.5 mEq/L), (c) WHF that required IV ambulatory diuretic, emergency department visit or HF rehospitalization at day 30, (d) CV mortality on day 30, and (e) all-cause mortality and HF hospitalization at day 30 (*Table 2*).

Table 2 Study endpoints of SALT-HF trial

Primary endpoint
Total diuresis after 3 h of the start of treatment
Secondary endpoints
• Change in body weight after 3 h.
• Cumulative natriuresis after 3 h.
• Change in body weight after 7 days.
• Change in congestion score after 7 days.
• Change in diameter of inferior vena cava after 7 days.
• Change in the presence of lung B-lines by echo after 7 days.
• Change in NYHA and visual analogue scale after 7 days.
• Change in biomarkers and hemoconcentration parameters (haematocrit, albumin, total proteins, natriuretic peptides, and CA125) after 7 days.
Safety endpoints
• Worsening kidney function, defined as an increase in serum creatinine $\geq$ 0.3 mg/d on day 7.
• Hypokalaemia in day 7 ($K^+ < 3.5$ mEq/L).
• Hyperkalaemia in day 7 (K+ $>$ 5.5 mEq/L).
• WHF that requires IV ambulatory diuretic, emergency department visit, or HF rehospitalization at day 30.
• CV mortality on day 30.
• All-cause mortality and HF hospitalization at day 30.

CA125, antigen carbohydrate 125; CV, cardiovascular; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Association; WHF, worsening heart failure.

Table 3 Procedures of SALT-HF trial

Visits	Visit 1: Screening and randomization	Visit 2: 3-h post-treatment	Visit 3: 7 days	Visit 4: 30 days
Eligibility	x			
Medical History	x			
NYHA	x		x	x
Visual analogue scale	x		x	
ECG	x		x	
Weight	x	x	x	
Blood pressure	x	x	x	
Diuresis		x		
Congestion score	x		x	
Local labs including haemoglobin, serum sodium, glucose, potassium, and kidney function measures	x		x	
NT-proBNP and CA125	x		x	
Urine sample	x	x	x	
Medication	x		X	x
Randomization	x			
Lung B-lines (echo)	x		x	
Inferior vena cava diameter	x		x	
Therapy optimization	x		x	x
Events including endpoints and adverse events			x	x

CA125, antigen carbohydrate 125; ECG, electrocardiogram; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Association.

Study intervention and procedures

The study flowchart is depicted in *Figure 1*, and a summary of the procedures in each visit is presented in *Table 3*.

Visit 1: Screening and randomization

Patients meeting the inclusion criteria, with prior informed consent, were randomized 1:1 to treatment with IV furosemide plus HSS (intervention group) versus IV furosemide (control group) using a stratified block randomization method based on an automated online system, blinded to the physicians who evaluated the patient. Randomization was performed by a trained HF nurse in a separate room. The patient and the treating physician were blinded to the assigned treatment.

Before the start of treatment, data were collected on patient demographics, medical history, and medical and device therapy at baseline. Blood and urine tests were collected at baseline and analysed in the local laboratory at each centre.

A complete clinical evaluation that included vital signs, ECG, NYHA functional class, a visual analogue scale from 0 (*worst state of health*) to 100 (*best state of health*),[14] and a congestion multiparametric assessment was performed.[15]

The multiparametric approach included

a The composite congestion score [composed of the sum of orthopnea (0–3; 0: *none*, 1: *seldom*, 2: *frequent*, 3: *continuous*), leg oedema (0–3; 0: *absent*, 1: *slight*, 2: *moderate*, 3: *marked*), and jugular engorgement (cm H_2O), (0–3; 0: ≤6, 1: 6–9, 2: 10–15, 3: ≥15)].[16]
b Imaging parameters as the inferior vena cava diameter and a protocolized evaluation of lung B-lines by ultrasound (Data S1). The presence of lung B-lines was considered positive when two lung fields presented ≥3 B-lines bilaterally.[17]
c Haematocrit, plasmatic albumin, and proteins as parameters of hemoconcentration.
d Biomarkers that included natriuretic peptides and CA125 plasmatic levels[18] and urinary sodium.

Treatment preparation and administration

After randomization, the HF nurse prepared the treatment in a separate room. The infusion consisted of a fixed furosemide dose that depended on the previous patient's home dose, administered in 100 mL of 0.9% NaCl physiological solution for 1 h (*Table 4*).

Patients with a home furosemide dose or equivalent equal to or inferior to 160 mg received 125 mg of furosemide. Patients with a home furosemide dose or equivalent superior to 160 mg received 250 mg of furosemide (*Table 4*). Torsemide was converted to the furosemide equivalent dose: 2 mg of oral furosemide was considered equivalent to 1 mg of oral torsemide.

In the absence of clear guidance from previous studies, or robust evidence supporting the use of double the home oral dose of loop diuretic, the SALT-HF diuretic dose strategy was based on local protocols that had previously evaluated the safety of this diuretic approach.[19]

In the group of patients randomized to HSS therapy, sodium chloride 200 mg/mL (10–15 mL) was added, depending on the patient's plasmatic sodium (2.6% HSS for patients with plasmatic sodium from 135 to 145 mEq/L, 3.4% HSS for patients with plasmatic sodium from 125 to 135 mEq/L).

Urine collection and sampling

Patients were asked to void empty before the administration of the infusion. From then on, the treatment, as well as the urine collection, started. The infusion was administered for 1 h, and the diuresis was collected for 3 h. Special care was taken to ensure that all urine was collected. The patient was advised to avoid food or liquid intake during this period.

The patients received the treatment and were monitored in a dedicated on-site IV infusion space. All the participant centers (n = 13, Data S2) have well-structured HF programmes led by specialized HF physicians and nurses.

Visit 2: 3-h post-treatment

Three hours after the start of the infusion, diuresis volume, blood pressure, and body weight were evaluated, and a new urine sample was collected.

To prevent heterogeneity in the treatment approach in the following days, we proposed a diuretic protocol adjustment at the time of discharge. Due to the potential risk of hypokalemia during diuretic treatment, the protocol also included recommendations about potassium supplements to mitigate the risk of hypokalaemia (Data S3).

Briefly, an increase in the diuretic treatment or combination therapy was recommended if no cause for decompensation was present. No other HF therapy modifications were allowed during the first 7 days.

Visit 3: 7-day post-treatment

Seven days after randomization, a new clinical and multiparametric evaluation that included all procedures of visit 1 was performed (*Table 3*). A 7-day evaluation was set to offer a pragmatic approach similar to real-life practice. Concomitant medication and adverse events, including any hospitalizations or deaths between treatment and day seven were recorded. Further therapy and changes in any medication at this stage were left to the treating physician's discretion.

Visit 4: 30-day post-treatment

Randomized patients were contacted by telephone 30 days following completion of the study treatment period to assess vital status, NYHA, the occurrence of adverse events, and current prescriptions for HF medications.

Table 4 Infusion preparation and placebo and treatment dose in SALT-HF trial

Patient oral daily dose	IV furosemide	1-h infusion	HSS group	Potassium supplements
Furosemide 80–160 mg Furosemide > 160 mg	125 mg 250 mg	100 ml of 0.9%NaCl physiological solution	Na^+: 125–135 mEq/L: 10 mL NaCl20% (2.6%) Na^+: 135–145 mEq/L: 15 ml NaCl20% (3.4%)	K^+: 3.5–4 mEq/L: 16–20 mEq of oral potassium.

HSS, hypertonic saline solution; IV, intravenous; po, orally.

Statistical plan

Sample size and power calculation

The SALT-HF trial was powered for its primary endpoint: diuresis after 3 h. Observational studies about diuretics in outpatients reported a 3-h diuresis of 1100 mL. A similar diuresis after 3 h was considered in the standard of care group (IV furosemide) for sample size calculation. An increase in diuresis of 20% was deemed both achievable and clinically relevant. Assuming a two-sided alpha of 0.05 and a statistical power of 80%, a sample size of 168 patients was calculated.

Statistical analysis

Continuous variables will be expressed as means (±1 standard deviation [SD]) or medians (interquartile range [IQR]), and discrete variables as percentages. At baseline, the means, medians, and frequencies between treatment groups will be compared using the *t*-test, Wilcoxon test, and chi-square test, respectively.

The primary endpoint (3-h diuresis) between treatments will be analysed by linear regression analysis. Secondary endpoints (changes in congestion, changes in kidney function, and changes in electrolytes) will be evaluated by linear regression analysis, including the baseline value of the endpoint as a covariate (ANCOVA). For 30-day adverse clinical events, a Cox regression analysis will be performed. Because of hierarchical levels of nesting (treatment sequence within patient ID and the latter among study centers), the models will include patient ID and study centre as random intercepts. All statistical comparisons will be performed under a modified intention-to-treat principle.

Current status

The SALT-HF trial is complete and is currently in the analysis phase. One hundred sixty-eight participants were randomized across 13 sites between December 4, 2020, and March 31, 2023. One patient had to be excluded due to screening failure (*Figure 2*). Baseline characteristics of the 167 patients did not present significant differences between the two groups across most parameters (*Table 5*). The SALT-HF trial encompassed an elderly population [median age: 81 years (IQR: 73–87), 30.5% females] with a high burden of co-morbidities such as diabetes, hypertension, atrial fibrillation, chronic obstructive pulmonary disease, and chronic kidney disease. Approximately half of the participants had an ejection fraction >50%. Most patients exhibited a poor functional NYHA class and several signs of congestion. Natriuretic peptides and CA125 were elevated at baseline. The chronic dose of diuretic was high (median furosemide dose: 120 mg), and the use of combination therapy was common (one-third of the patients were on treatment with SGLT2i and/or thiazides and half of them received mineralocorticoid receptor antagonists).

Discussion

The SALT-HF trial will evaluate whether HSS plus IV furosemide therapy is safe and more effective in improving diuretic response than IV furosemide in ambulatory patients suffering WHF, a subgroup frequent in clinical practice but underrepresented in clinical trials. The ultimate goal is to provide novel insights into diuretic strategies that may help relieve congestion and prevent HF hospitalizations.

Outpatient management of worsening heart failure

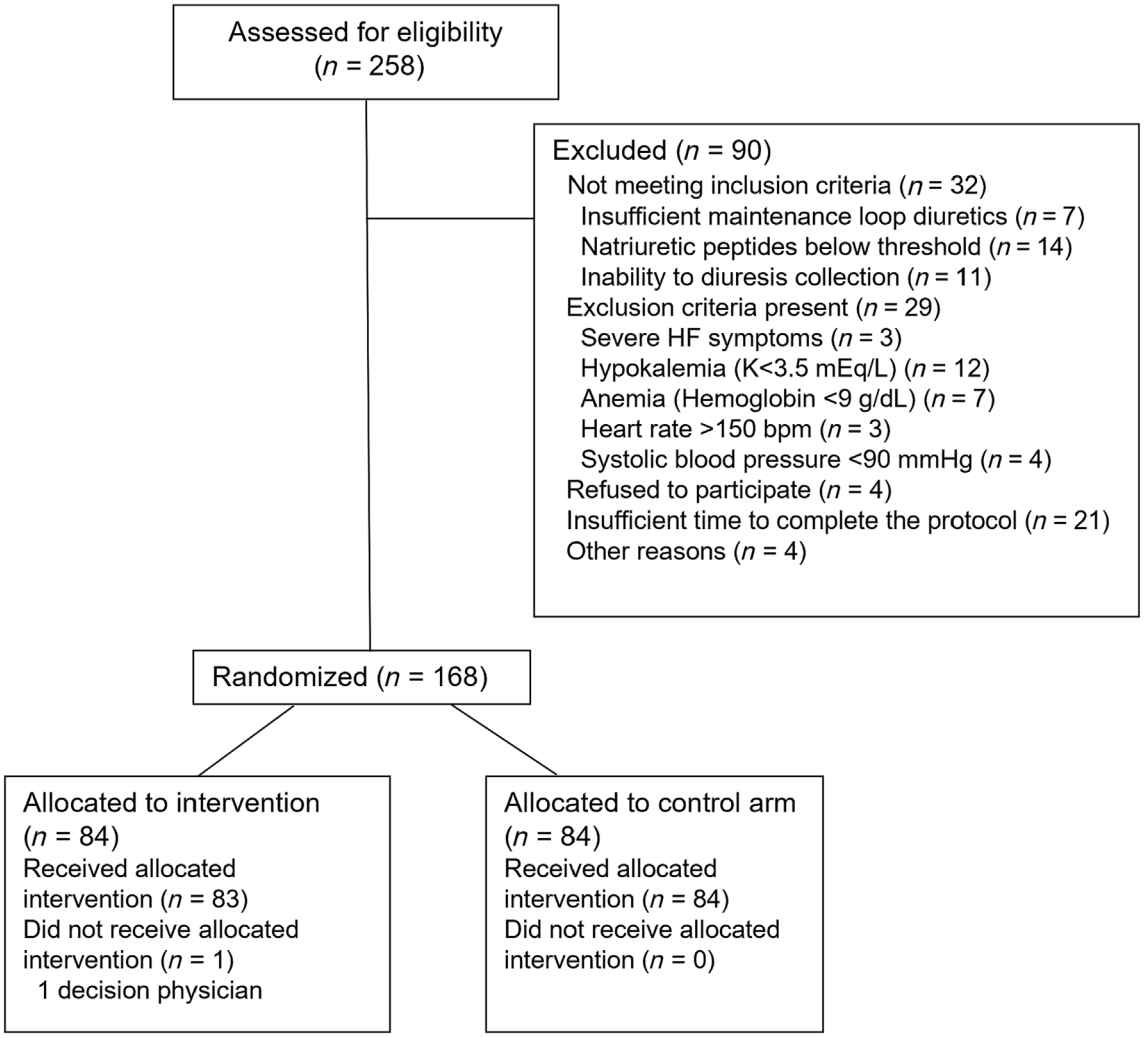
A substantial rise in HF burden in the Western population is projected for the next decades.[20] We observed that patients included in the SALT-HF trial were significantly older and had more co-morbidities than previously reported series of ambulatory HF patients.[10] Beyond the significant burden on healthcare costs, HF hospitalizations are associated with a further increased risk of death and worsening quality of life.[21–23] Therefore, a shift from the classic hospital-centric model to ambulatory WHF management strategies is of growing interest to both patients and healthcare providers.

Multidisciplinary HF management programmes are recommended (class IA) in HF guidelines to reduce hospitalizations and mortality.[11,12] Even though guidelines describe the characteristics and components of HF programmes, they do not provide any recommendations about diuretic approaches for ambulatory worsening HF, and the management of these patients remains empirical. To address this gap, the Heart Failure Working Group of the French Society of Cardiology has recently published a document about the practical outpatient management of WHF.[2] The document defines 'outpatient HF' as the worsening of HF signs and symptoms in a patient with chronic HF that requires escalation of therapy without an urgent need for hospitalization. The stratification of patients who will not require hospital admission in the first instance is one of the key elements for a successful ambulatory approach. Determinant clinical scenarios, HF profiles, co-morbidities, and social criteria should be considered to determine the feasibility and safety of outpatient management. SALT-HF inclusion and exclusion criteria define the clinical profile most likely to fit an ambulatory IV diuretic programme.

Diuretic approach in the outpatient setting

Unfortunately, limited data exist regarding IV diuretic strategies and outcomes in ambulatory WHF. The document about the practical outpatient management of WHF proposes a standardized diuretic protocol based on data from the largest study that has evaluated an outpatient IV diuretic approach.[2]

Figure 2 Flow diagram of patient inclusion.



Briefly, Buckley et al. assessed the diuretic response and outcomes in 283 patients with WHF.[1] The diuretic protocol consisted of a 3-h IV diuretic infusion based on the furosemide equivalent of patient's home oral diuretic total daily dose. This strategy was associated with significant urine output and weight loss. This and other observational studies suggest that an IV-diuretic ambulatory approach may provide an alternative to hospitalization for the management of selected patients with HF.[3,4]

On the other hand, diuresis after 3 h of treatment was selected as the primary endpoint of our study because (i) urinary output is commonly used as a metric of loop diuretic efficacy,[24] (ii) the direct effect of loop diuretics is increasing diuresis,[25] (iii) urinary output is an objective and reproducible endpoint, not open for bias, (iv) 3-h diuresis has been evaluated in observational studies assessing ambulatory diuretic treatment.[1,5]

Hypertonic saline therapy in worsening heart failure

Observational studies, randomized trials, and metanalysis have shown the potential benefits of HSS plus IV loop diuretic in improving diuretic response, kidney function, and outcomes in patients hospitalized with WHF.[10,26,27]

However, the differences in the population included in the studies and the heterogeneity in the infusion preparation or the diuretic dose (Data S4) have limited the adoption of this therapy in clinical practice. In addition, many physicians often struggle with administering sodium in patients who present with fluid overload. We specifically excluded patients with pulmonary oedema or low oxygen saturation.

Therefore, in this trial, we will assess the efficacy and safety of this therapeutical approach in patients with predominant tissue systemic volume overload, which includes

Table 5 Baseline demographics and clinical characteristics of the SALT-HF trial population

Parameter	Statistic	SALT-HF trial (*N* = 167)	HSS + furosemide (*n* = 83)	IV furosemide (*N* = 84)	*P*-value
Demographics and medical history					
Age (years)	Median (IQR)	81 (73–87)	83 (74–88)	80 (73–86)	0.072
Female	*n* (%)	51 (30.5)	27 (32.5)	24 (28.5)	0.579
Charlson index	Median (IQR)	3 (2–4)	3 (2–4)	3 (2–4)	0.677
Diabetes mellitus	*n* (%)	69 (41.4)	32 (38.5)	37 (44.0)	0.398
Hypertension	*n* (%)	143 (85.6)	68 (81.9)	75 (89.3)	0.175
Hypercholesterolemia	*n* (%)	93 (55.7)	39 (46.9)	54 (64.3)	0.024
Atrial fibrillation	*n* (%)	134 (80.2)	66 (9.5)	68 (80.9)	0.816
COPD	*n* (%)	49 (29.3)	25 (30.1)	24 (28.6)	0.826
CKD	*n* (%)	107 (64.5)	50 (60.1)	57 (67.8)	0.279
Ischaemic cardiomyopathy	*n* (%)	48 (28.7)	21 (25.3)	27 (32.1)	0.928
Valvular heart disease	*n* (%)	34 (20.4)	24 (28.9)	10 (11.9)	0.133
Vital signs and basal assessment					
NYHA	*n* (%)				0.907
I		3 (1.8)	2 (2.4)	1 (1.2)	
II		46 (27.5)	24 (28.9)	22 (26.2)	
III		116 (69.5)	56 (67.4)	60 (71.4)	
IV		2 (1.2)	1 (1.2)	1 (1.2)	
Analogue visual scale	Mean (SD)	54.6 (18.7)	55.4 (19.0)	53.8 (18.4)	0.695
Composite congestion score	Mean (SD)	4.3 (1.7)	4.2 (1.7)	4.3 (1.6)	0.651
Jugular engorgement	*n* (%)	151(91.4)	74 (89.2)	77 (91.2)	0.582
Orthopnoea	*n* (%)	113 (67.7)	53 (63.9)	60 (71.4)	0.296
Lower limb oedema	*n* (%)	151 (90.4)	78 (90.4)	73 (86.9)	0.121
Systolic blood pressure (mmHg)	Median (IQR)	118 (107–131)	116 (105–128)	122 (110–133)	0.022
Heart rate (b.p.m.)	Median (IQR)	70 (65–81)	71 (65–82)	70 (63–80)	0.540
Weight (kg)	Median (IQR)	76.3 (66.5–86)	74.9 (65.0–84.8)	78.0 (68.5–88.0)	0.236
Echocardiography					
LVEF (%)	Median (IQR)	50 (38–60)	50 (40–60)	50 (35–60)	0.453
HFrEF	*n* (%)	44 (26.3)	20 (24.1)	24 (28.5)	0.602
HFmEF	*n* (%)	41 (24.6)	23 (27.7)	18 (21.4)	
HFpEF	*n* (%)	82 (49.1)	40 (48.1)	42 (50.0)	
Inferior vena cava (mm)	Median (IQR)	23 (21–25)	23 (21–26)	23 (21–25)	0.457
Presence of lung B lines[a]	*n* (%)	118 (71.0)	59 (71.0)	59 (70.2)	1.000
Laboratory data					
Haemoglobin (g/dL)	Median (IQR)	12.0 (10.8–13.4)	11.7 (10.8–13.0)	12.1 (10.8–13.7)	0.560
Haematocrit (%)	Median (IQR)	36.9 (33.2–42.0)	36.9 (34–41.9)	37.0 (33.0–43.0)	0.941
eGFR (mL/min/1.73m^2)	Median (IQR)	40.2 (29.3–53.1)	40.3 (29.4–54.6)	39.1 (28.7–52.2)	0.354
Creatinine (mg/dL)	Median (IQR)	1.5 (1.1–1.9)	1.5 (1.1–1.8)	1.5 (1.2–2.0)	0.160
Sodium (mEq/L)	Median (IQR)	140 (137–141)	140 (137–142)	139 (137–141)	0.803
Potassium (mEq/L)	Median (IQR)	4.2 (3.9–4.5)	4.2 (3.9–4.5)	4.1 (3.7–4.4)	0.220
Chloride (mEq/L)	Median (IQR)	101 (99–104)	101 (99–104)	100 (98–104)	0.239
NT-proBNP (pg/mL)	Median (IQR)	4969 (2508–9328)	5302 (2467–9790)	4851 (2546–8770)	0.875
CA125 (U/mL)	Median (IQR)	46 (20–114)	40 (20–94)	56 (19–123)	0.630
Urinary sodium (mEq/L)	Median (IQR)	67 (43–88)	70 (48–89)	65 (36–88)	0.379
Treatment					
Furosemide (mg)	Median (IQR)	120 (80–160)	120 (80–160)	120 (80–160)	0.117
Thiazides	*n* (%)	47 (28.1)	25 (30.1)	22 (26.2)	0.572
Mineral receptor antagonists	*n* (%)	81 (48.5)	36 (43.4)	45 (53.6)	0.187
Acetazolamide	*n* (%)	8 (4.8)	5 (6.2)	3 (3.6)	0.469
Beta-blockers	*n* (%)	116 (69.5)	60 (72.3)	56 (66.7)	0.430
RAASi	*n* (%)	91 (54.5)	47 (56.6)	44 (52.3)	0.582
SGLT2i	*n* (%)	61 (36.5)	25 (30.1)	36 (42.9)	0.087

CA125, antigen carbohydrate 125; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HFmEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RAASi, renin-angiotensin-aldosterone system inhibitors; SGLT2i, sodium-glucose co-transporter-2 inhibitors.
[a]Considered positive when ≥3 B-lines were bilaterally observed in ≥2 lung fields.

patients with lower limb oedema, ascites, and/or pleural effusion. We hypothesize that the administration of HSS may improve the diuretic effectiveness of furosemide in patients with predominant extravascular and systemic volume overload. The rationale of this approach is the osmotic capacity of HSS, which leads to fluid mobilization from the interstitial space into the intravascular compartment, increasing intravascular volume and renal blood flow and facilitating the delivery of the diuretic agents to the nephron.[28] Although some research suggests that the blunted diuretic response observed in chronic furosemide users is primarily due to decreased tubular responsiveness rather than insufficient

furosemide tubular delivery,[29] we speculate that the volume expansion and the action of IV furosemide will lead to a more efficient diuretic response in a cohort of patients with data of diuretic resistance.

Notably, the administration of chloride together with sodium may also play a role in the potential benefits of this therapy in HF patients. Several observational studies have shown the association of low chloride levels with poor diuretic response, increased neurohormonal activation, and a worse prognosis.[30] The cardiorenal effects of sodium-free chloride supplementation are currently being tested in patients with ADHF. (Mechanism and Effects of Manipulating Chloride Homeostasis in Stable Heart Failure; NCT03440970).

The hypothesis that will be tested in the SALT-HF trial is important in several aspects. First, there is a growing need for strategies that prevent HF hospitalizations. Second, to our knowledge, no randomized trials evaluating diuretic strategies in the outpatient setting have been performed, and treatment remains empirical. Finally, although HSS therapy appears to be a promising strategy to overcome diuretic resistance, a growing body of evidence supporting the beneficial effects may promote implementing this approach in outpatient WHF patients.

Conclusions

The SALT-HF trial will investigate whether a combined therapy of IV furosemide with HSS can increase diuresis after 3 h compared with IV furosemide in ambulatory patients with WHF and systemic fluid overload.

Funding

This work was partially supported by grants from the Instituto de Salud Carlos III (PI20/00689). (Co-funded by European Regional Development Fund/European Social Fund 'A way to make Europe'/'Investing in your future').

Conflict of interest

None declared. All the authors have approved the manuscript.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1: *Assessment of* B-lines with lung ultrasound.
Data S2: Participant Centers of SALT-HF trial.
Data S3: Diuretic protocol at discharge.
Data S4: Hypertonic saline solution and diuretic dose in different trials.

References

1. Buckley LF, Stevenson LW, Cooper IM, Knowles DM, Matta L, Molway DW, *et al*. Ambulatory treatment of worsening heart failure with intravenous loop diuretics: A four-year experience. *J Card Fail* 2020;**26**:798-799. doi:10.1016/j.cardfail.2019.10.015
2. Girerd N, Mewton N, Tartière JM, Guijarro D, Jourdain P, Damy T, *et al*. Practical outpatient management of worsening chronic heart failure. *Eur J Heart Fail* 2022;**24**:750-761. doi:10.1002/ejhf.2503
3. Hebert K, Dias A, Franco E, Tamariz L, Steen D, Arcement LM. Open access to an outpatient intravenous diuresis program in a systolic heart failure disease management program. *Congest Heart Fail* 2011;**17**:309-313. doi:10.1111/j.1751-7133.2011.00224.x
4. Ryder M, Murphy NF, McCaffrey D, O'Loughlin C, Ledwidge M, McDonald K. Outpatient intravenous diuretic therapy; potential for marked reduction in hospitalisations for acute decompensated heart failure. *Eur J Heart Fail* 2008;**10**:267-272. doi:10.1016/j.ejheart.2008.01.003
5. Buckley LF, Carter DM, Matta L, Cheng JW, Stevens C, Belenkiy RM, *et al*. Intravenous diuretic therapy for the management of heart failure and volume overload in a multidisciplinary outpatient unit. *JACC Heart Fail* 2016;**4**:-8. doi:10.1016/j.jchf.2015.06.017
6. Griffin M, Soufer A, Goljo E, Colna M, Rao VS, Jeon S, *et al*. Real world use of hypertonic saline in refractory acute decompensated heart failure: A U.S. center's experience. *JACC Heart Fail* 2020;**8**:199-208. doi:10.1016/j.jchf.2019.10.012
7. De Vecchis R, Esposito C, Ariano C, Cantatrione S. Hypertonic saline plus i.v. furosemide improve renal safety profile and clinical outcomes in acute decompensated heart failure: A meta-analysis of the literature. *Herz* 2015;**40**:423-435. doi:10.1007/s00059-013-4041-6
8. Gandhi S, Mosleh W, Myers RBH. Hypertonic saline with furosemide for the treatment of acute congestive heart failure: A systematic review and meta-analysis. *Int J Cardiol* 2014;**173**:139-145. doi:10.1016/j.ijcard.2014.03.020
9. Licata G, Di Pasquale P, Parrinello G, Cardinale A, Scandurra A, Follone G, *et al*. Effects of high-dose furosemide and small-volume hypertonic saline solution infusion in comparison with a high dose of furosemide as bolus in refractory congestive heart failure: long-term effects. *Am Heart J* 2003;**145**:459-466. doi:10.1067/mhj.2003.166
10. Paterna S, Fasullo S, Parrinello G, Cannizzaro S, Basile I, Vitrano G, *et al*. Short-term effects of hypertonic saline solution in acute heart failure and long-term effects of a moderate sodium

restriction in patients with compensated heart failure with New York heart association class III (class C) (SMAC-HF study). *Am J Med Sci* 2011;**342**:27-37.
11. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *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
12. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, *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. *J Am Coll Cardiol [Internet]* 2022; **79**:e263-e421.
13. Bozkurt B, Coats AJ, Tsutsui H, Abdelhamid M, Adamopoulos S, Albert N, *et al*. Universal Definition and Classification of Heart Failure: A report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. *J Card Fail [Internet]* 2021;**27**:387-413. doi:10.1002/ejhf.2115
14. Measurement of feelings using visual analogue scales - PubMed.
15. de la Espriella R, Cobo M, Santas E, Verbrugge FH, Fudim M, Girerd N, *et al*. Assessment of filling pressures and fluid overload in heart failure: An updated perspective. *Rev Esp Cardiol (Engl Ed)* 2023;**76**:47-57. doi:10.1016/j.rec.2022.07.009
16. Ambrosy AP, Pang PS, Khan S, Konstam MA, Fonarow GC, Traver B, *et al*. Clinical course and predictive value of congestion during hospitalization in patients admitted for worsening signs and symptoms of heart failure with reduced ejection fraction: Findings from the EVEREST trial †. *Eur Heart J* 2013;**34**: 835-843. doi:10.1093/eurheartj/ehs444
17. Volpicelli G, Elbarbary M, Blaivas M, Lichtenstein DA, Mathis G, Kirkpatrick AW, *et al*. International evidence-based recommendations for point-of-care lung ultrasound. *Intensive Care Med* 2012;**38**: 577-591. doi:10.1007/s00134-012-2513-4
18. Núñez J, de la Espriella R, Miñana G, Santas E, Llácer P, Núñez E, *et al*. Antigen carbohydrate 125 as a biomarker in heart failure: a narrative review. *Eur J Heart Fail* 2021;**23**:1445-1457. doi:10.1002/ejhf.2295
19. Portolés A, Cobo M, Zegrí, Vázquez López-Ibor J, Soria Gómez T, Escobar López LE, *et al*. Eficacia y seguridad de la furosemida intravenosa junto con suero salino hipertónico en el paciente ambulatorio con insuficiencia cardiaca descompensada. *Rev Esp Cardiol* 2020; **73**:434.
20. Roger VL. Epidemiology of heart failure: a contemporary perspective. *Circ Res* 2021;**128**:1421-1434. doi:10.1161/CIRCRESAHA.121.318172
21. Setoguchi S, Stevenson LW, Schneeweiss S. Repeated hospitalizations predict mortality in the community population with heart failure. *Am Heart J* 2007; **154**:260-266. doi:10.1016/j.ahj.2007.01.041
22. Nieminen MS, Dickstein K, Fonseca C, Serrano JM, Parissis J, Fedele F, *et al*. The patient perspective: Quality of life in advanced heart failure with frequent hospitalisations. *Int J Cardiol* 2015;**191**: 256-264. doi:10.1016/j.ijcard.2015.04.235
23. Ambrosy AP, Khan H, Udelson JE, Mentz RJ, Chioncel O, Greene SJ, *et al*. Changes in dyspnea status during hospitalization and postdischarge health-related quality of life in patients hospitalized for heart failure: findings from the EVEREST trial. *Circ Heart Fail* 2016;**9**: doi:10.1161/CIRCHEARTFAILURE.115.002458
24. Testani JM, Brisco MA, Turner JM, Spatz ES, Bellumkonda L, Parikh CR, *et al*. Loop diuretic efficiency: A metric of diuretic responsiveness with prognostic importance in acute decompensated heart failure. *Circ Heart Fail* 2014;**7**:261-270. doi:10.1161/CIRCHEARTFAILURE.113.000895
25. 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
26. Lafrenière G, Béliveau P, Bégin JY, Simonyan D, Côté S, Gaudreault V, *et al*. Effects of hypertonic saline solution on body weight and serum creatinine in patients with acute decompensated heart failure. *World J Cardiol* 2017;**9**: 685-692. doi:10.4330/wjc.v9.i8.685
27. Yayla Ç, Akyel A, Canpolat U, Gayretli Yayla K, Eyiol A, Akboğa MK, *et al*. Comparison of three diuretic treatment strategies for patients with acute decompensated heart failure. *Herz* 2015; **40**:1115-1120. doi:10.1007/s00059-015-4327-y
28. Mazzoni MC, Borgstrom P, Arfors KE, Intaglietta M. Dynamic fluid redistribution in hyperosmotic resuscitation of hypovolemic hemorrhage. *Am J Physiol* 1988;**255**:H629-H637. doi:10.1152/ajpheart.1988.255.3.H629
29. Biegus J, Zymliński R, Testani J, Fudim M, Cox ZL, Guzik M, *et al*. The blunted loop diuretic response in acute heart failure is driven by reduced tubular responsiveness rather than insufficient tubular delivery. The role of furosemide urine excretion on diuretic and natriuretic response in acute heart failure. *Eur J Heart Fail* 2023;**25**:1323-1333. doi:10.1002/ejhf.2852
30. Ter Maaten JM, Damman K, Hanberg JS, Givertz MM, Metra M, O'Connor CM, *et al*. Hypochloremia, diuretic resistance, and outcome in patients with acute heart failure. *Circ Heart Fail* 2016;**9**: doi:10.1161/CIRCHEARTFAILURE.116.003109