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CLINICAL RESEARCH
Heart failure and cardiomyopathies

Combining loop with thiazide diuretics for decompensated heart failure: the CLOROTIC trial

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Abstract

Aims To evaluate whether the addition of hydrochlorothiazide (HCTZ) to intravenous furosemide is a safe and effective strategy for improving diuretic response in acute heart failure (AHF).

Methods and results A prospective, double-blind, placebo-controlled trial, including patients with AHF randomized to receive HCTZ or placebo in addition to an intravenous furosemide regimen. The coprimary endpoints were changes in body weight and patient-reported dyspnoea 72 h after randomization. Secondary outcomes included metrics of diuretic response and mortality/rehospitalizations at 30 and 90 days. Safety outcomes (changes in renal function and/or electrolytes) were also assessed. Two hundred and thirty patients (48% women, 83 years) were randomized. Patients assigned to HCTZ were more likely to lose weight at 72 h than those assigned to placebo [−2.3 vs. −1.5 kg; adjusted estimated difference (notionally 95% confidence interval) −1.14 (−1.84 to −0.42); $P = 0.002$], but there were no significant differences in patient-reported dyspnoea (area under the curve for visual analogue scale: 960 vs. 720; $P = 0.497$). These results were similar 96 h after randomization. Patients allocated to HCTZ showed greater 24 h diuresis (1775 vs. 1400 mL; $P = 0.05$) and weight loss for each 40 mg of furosemide (at 72 and at 96 h) ($P < 0.001$). Patients assigned to HCTZ more frequently presented impaired renal function (increase in creatinine >26.5 μmoL/L or decrease in eGFR >50%; 46.5 vs. 17.2%; $P < 0.001$), but hypokalaemia and hypokalaemia were similar between groups. There were no differences in mortality or rehospitalizations.

Conclusion The addition of HCTZ to loop diuretic therapy improved diuretic response in patients with AHF.

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Structured Graphical Abstract

Key Question

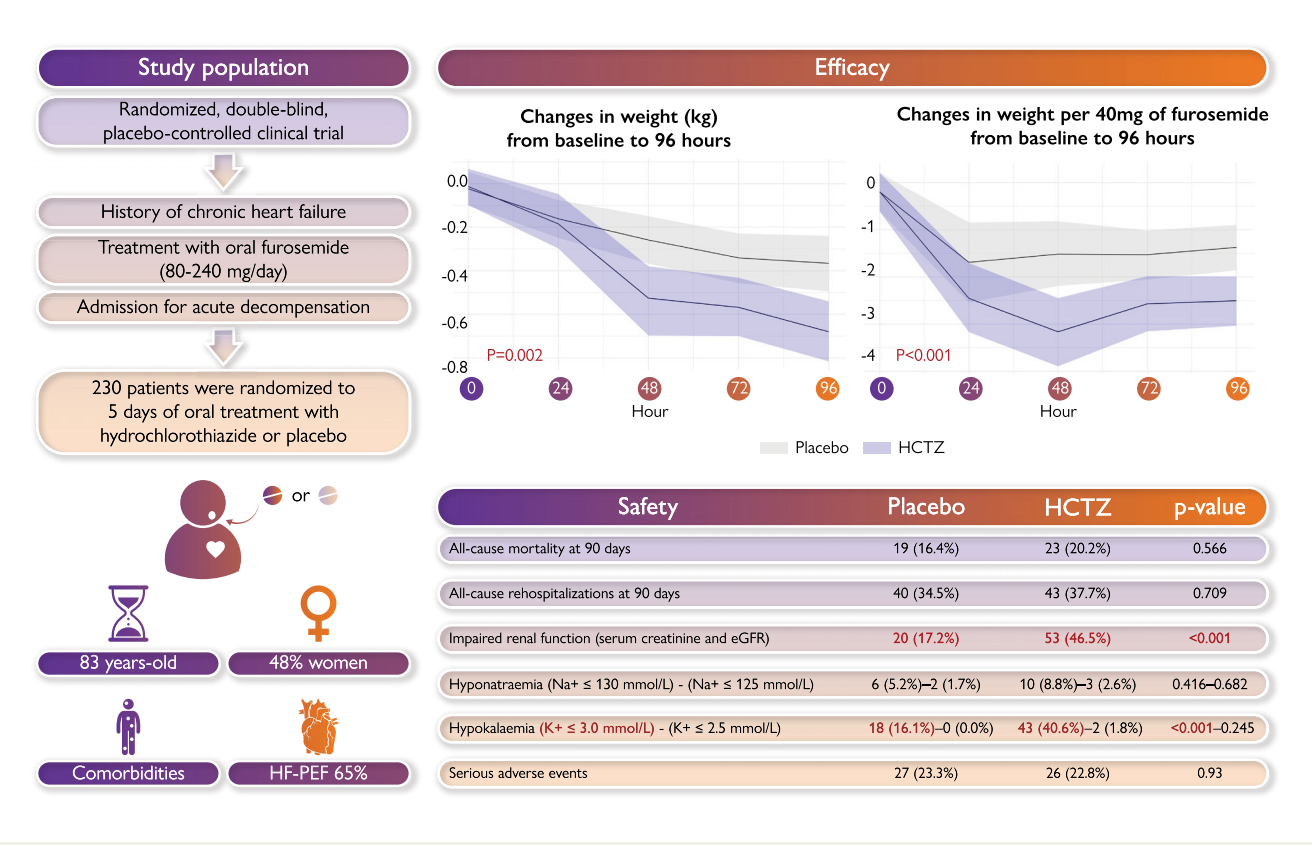
Does the addition of hydrochlorothiazide to standard intravenous loop-diuretic therapy improve the diuretic response in patients with acute heart failure (AHF)?

Key Finding

In patients with AHF, the combination of oral hydrochlorothiazide with intravenous loop diuretics improved the diuretic response but was associated with worsening renal function.

Take Home Message

The addition of hydrochlorothiazide to intravenous loop diuretics improves the diuretic response in patients with decompensated heart failure at the cost of worsening renal function.



Graphical summary of the design and main findings of the CLOROTIC trial

Keywords Heart failure • Diuretics • Thiazides • Hydrochlorothiazide • Furosemide

Introduction

Acute heart failure (AHF) is the leading cause of hospitalization in older people and accounts for the highest healthcare costs in the USA and in Europe.[1] The number of individuals with heart failure (HF) will increase steadily over the next 20 years, largely due to the ageing of the population and changes in the epidemiology of common risk factors for HF.[1,2] The vast majority of patients admitted for AHF are treated primarily with intravenous loop diuretics, while prospective trial data evaluating the efficacy or safety of different diuretic strategies are limited. Consequently, current guidelines in this area are based primarily on expert opinion.[3]

An important and challenging subset of patients with AHF exhibit fluid overload despite significant doses of loop diuretics. The pathophysiology of diuretic resistance includes increased distal nephron

sodium absorption in the case of (prolonged) loop diuretic administration.[4] One approach to overcoming loop diuretic resistance is the addition of a thiazide diuretic to produce diuretic synergy via sequential nephron blockade. This approach may potentially induce diuresis in patients otherwise resistant to loop diuretics, but it has not been properly evaluated in multicentre clinical trials designed to establish safety and clinical efficacy.[4] Moreover, in view of the relative safety of high-dose loop diuretics in the DOSE-AHF trial,[5] expert recommendations have given preference to initial intensification of the loop diuretic dose before adding a thiazide diuretic.[6]

As the role of combined diuretic therapy in AHF remains uncertain, we conducted the Safety and Efficacy of the Combination of Loop with Thiazide-type Diuretics in Patients with Decompensated Heart Failure (CLOROTIC) trial to evaluate whether the addition of hydrochlorothiazide (HCTZ) to intravenous furosemide is a safe and effective strategy for improving diuretic response in patients with AHF.

Methods

Study design

The CLOROTIC study was a multicentre, prospective, randomized, double-blind, placebo-controlled trial,[7] designed, conducted, and funded by the Heart Failure Working Group of the Spanish Society of Internal Medicine. The Biomedical Research Institute (IRB, Lleida, Spain) was responsible for data management and statistical analysis. The study protocol, including the statistical analysis plan, has been described elsewhere.[7] The study complies with the Declaration of Helsinki and was approved by the Spanish Agency for Medication and Healthcare Products and the local institutional ethics committees at each centre. All patients provided written informed consent (ClinicalTrials.gov identifier: NCT01647932; EudraCT Number: 2013-001852-36).

Study participants

Patients (men and women) were eligible for enrolment if they were 18 years of age or older, had a history of chronic HF (with no pre-specified inclusion criterion for HF aetiology and/or ejection fraction) and had been hospitalized within the previous 24 h for acute decompensated HF. No minimum volume overload was required at the time of inclusion. Additional eligibility criteria were treatment with an oral loop diuretic, for at least 1 month before hospitalization, at a furosemide dose between 80 and 240 mg daily, or an equivalent dose in the case of a different loop diuretic. Patients were excluded if they were unstable on admission (acute coronary syndrome, cardiogenic shock, and/or intensive care unit admission), treated with inotropic agents (other than digoxin) or with any thiazide diuretic during the month before admission (aldosterone antagonists were permitted if the patient had been receiving them on a long-term basis). Renal failure was not an exclusion criterion (being accepted any value of glomerular filtration rate upon admission) except if the patient required renal replacement therapy. Hypokalaemia and hyponatraemia were an exclusion criteria if potassium or sodium values at randomization were equal or below 2.5 or 125 mmoL/L (or any symptomatic sodium value), respectively.

Randomization and treatment assignments

Patients were randomly assigned, on a 1:1 ratio, to receive HCTZ or placebo for 5 days, supplied as oral tablets. For each recruiting centre, a random sequence of five blocks of size 4 (20 units in total) was generated. Patients were randomized within the first 24 h after hospital admission, and the study medication (or placebo) and concomitant intravenous furosemide were administered immediately after randomization.

Oral HCTZ and placebo doses were adjusted according to glomerular filtration rate, estimated using the Modification of Diet in Renal Disease formula, as follows: > 50 mL/min: 25 mg daily; 20–50 mL/min: 50 mg daily; and <20 mL/min: 100 mg daily.[8] Patients received the same HCTZ (or placebo) dose during the treatment period, and up-titration or down-titration was not permitted at investigators discretion. The dose of HCTZ (or placebo) could only be adjusted based on changes in glomerular filtration rate observed during the treatment period. To ensure homogeneous intravenous loop diuretic administration in all participating centres, an algorithm for furosemide dosage (according to the low dose arm of the DOSE-AHF trial[5]) was recommended in the protocol (see Supplementary material online, *Table S1*).

All patients were monitored during the study medication period, until hospital discharge and then for an additional safety period of 90 days after discharge. Patients had to be admitted and could not be discharged during the 5-day randomized treatment period for close monitoring of adverse effects.

Endpoints

The trial had two coprimary endpoints. The primary efficacy endpoints were changes in body weight and changes in patient-reported dyspnoea from baseline to 72 h of randomization. Patient-reported dyspnoea was assessed with the use of a visual analogue scale (VAS) and quantified as the area under the curve (AUC) of serial assessments from baseline to 72 h.

Pre-specified secondary endpoints included the following: changes in body weight and patient-reported dyspnoea 96 h after randomization (using the VAS and the Likert 7-point scales), metrics of diuretic response, hospital length of stay, mortality, and rehospitalizations (all-cause and HF-related) at 30 and 90 days. The metrics of diuretic response included 24 h diuresis quantification, weight loss per 40 mg of furosemide (at 72 and at 96 h), net fluid loss (24 h diuresis) per milligram of furosemide and mean loop diuretic dose administered from time of study enrolment to 72 h.

Body weight was measured using the same scale for all weight determinations made during the study. For the quantification of 24 h diuresis bladder catheterization was not mandatory and only performed at clinical judgement of each investigator and according to their usual clinical practice.

For the VAS, patients were asked to evaluate their perceived dyspnoea by marking a 10 cm vertical line, with the top labelled 'I can't breathe at all' and the bottom labelled 'I can breathe normally'. We scored the patients' markings on a scale of 0–100 by measuring the distance in millimetres from the bottom of the line. The 7-point Likert scale was used to determine changes from baseline: (1) much worse, (2) moderately worse, (3) a little worse, (4) no change, (5) a little better, (6) moderately better, and (7) much improved.

Safety endpoints were changes in renal function and changes in electrolyte levels (sodium and potassium). Impaired renal function was defined as an increase in serum creatinine levels >26.5 μmoL/L or a decrease in serum estimated glomerular filtration rates higher than 50% compared with baseline levels. Hypokalaemia and hyponatraemia were defined as potassium levels equal or lower than 2.5 mmoL/L and sodium levels equal or lower than 125 mmoL/L, respectively. In addition, the appearance of any adverse event was precisely analysed and recorded at every study visit. Hypotension was defined as a systolic blood pressure of <90 mmHg or any symptomatic drop in systolic blood pressure.

Sample size

Based on previous studies, we estimated that with a sample of 304 patients, the study would have a minimum 85% power to detect a clinically relevant difference at 72 h between groups in body weight loss [mean (SD) of 2.5 (4.5) kg] and perceived dyspnoea on the VAS [mean (SD) of 1476 (2080) $mm \cdot h^{-1}$] with a global Type I error rate of 5% after Bonferroni correction and an expected dropout rate of 8%.[5,9–11] Due to slow recruitment, the study was terminated early, reaching a sample size of 230 patients.

Statistical analysis

All analyses were performed according to the intention-to-treat principle. Missing values in the primary outcome variables were interpolated if measures were available before and after the missing values. If no measure was

available after a missing value, the last observation carried forward method was applied. A sensitivity analysis was performed using multiple imputation by chained equations (five imputed values per missing value) applying the method of predictive mean matching iteratively until convergence to both continuous primary outcomes. Summary measures of mean (standard deviation) and median (interquartile interval) were used for quantitative variables with and without a normal distribution, respectively. The AUC for dyspnoea VAS scores changes from baseline throughout the study was estimated by applying the trapezoidal rule after missing imputation. Quantitative outcomes and their changes from baseline were compared between groups using the Student's *t*-test if normally distributed or the Mann–Whitney's *U* test otherwise. Qualitative outcomes were compared between groups using Pearson's χ^2 test (or Fisher's exact test if expected frequencies lower than 5). Mean changes from randomization and throughout the study in both primary endpoints (weight loss and dyspnoea VAS score changes) and also in weight loss per 40 mg of furosemide were represented graphically and estimated by linear mixed-effects models with the random effect of patient and the interaction between the fixed effects of group and time. No form of trend was assumed for time, introducing it as a qualitative variable into the models. The identified unbalanced variables at baseline were added to the mixed-effects models to subtract their possible additive effect from the treatment effect estimation. For the mean of weight loss, an analysis of interactions between the randomized group and baseline variables (categorizing them into binary variables of interest or based on their median values) was done by modelling their second order interaction with group and time. The estimated difference in weight loss mean at 72 h for HCTZ vs. placebo in each category of baseline variables, together with the estimated difference between categories were graphically represented in a forest plot. A non-parametric cases bootstrap 97.5% CI based on 5000 replicates (resampling patients) was added to the mean estimates in each figure based on mixed-effects models.

Overall survival, hospital readmission-free survival and the post-hoc combined endpoint (death or readmission) in both groups was graphically represented using Kaplan–Meier curves and compared by Cox proportional hazards regression models until 90 days of follow-up after hospital discharge. For both analysis, time started on the day of randomization. A Fine and Grey competing risk analysis and a cumulative incidence plot for the hospital readmission-free survival was also analysed for the subgroup of participants being discharged, where time started on the day of hospital discharge and deaths that occurred along follow-up were taken as competing events.

All statistical analysis were performed in R, applying a significance level of 0.025 (and therefore having a 97.5% confidence, notionally 95%) for the two coprimary outcomes and 0.05 for secondary and safety outcomes. Secondary and safety outcomes statistical analysis were not adjusted for multiple testing.

Results

Patient population

A total of 6914 patients underwent screening, and after 230 patients were included (between October 2014 and October 2019 at 26 clinical sites in Spain) the inclusion has to be halted due to slow enrolment (see Supplementary material online, *Appendix* and *Figure S1*). Baseline characteristics for each of the treatment groups are shown in *Table 1*. The median age of the patients was 83 years and 111 (48%) were women. According to New York Heart Association functional class, most patients were on Class III (51%) or IV (10%), and the remaining were mildly symptomatic at baseline. The patient population had a high burden of comorbidities and high-risk features, including a history of hospitalization for HF within the previous 12 months (138, 60% of the patients), moderate renal dysfunction (median estimated glomerular filtration rate, 43 mL/min/1.73 m^2), and elevated natriuretic peptide levels (median N-terminal pro-B-type natriuretic peptide level, 4672 pg/mL). Patient characteristics at baseline were balanced between the two treatment groups, except for differences in gender, systolic blood pressure, body mass index (differences in height, not weight), and ischaemic cause of HF. The mean ejection fraction was 55% and 143 (65.3%) of patients had an ejection fraction of 50% or greater.

Endpoints

After adjusting for unbalanced baseline characteristics, patients assigned to HCTZ were more likely to lose weight 72 h after randomization than those assigned to placebo [−2.3 vs. −1.5 kg; adjusted estimated difference (notionally 95% CI) −1.14 (−1.84 to −0.42); $P = 0.002$]. There were no significant differences in patient-reported dyspnoea in the HCTZ group compared with placebo [mean AUC at 72 h using VAS was 960 (360–1620) vs. 720 (240–1455), respectively; $P = 0.497$]. These results were similar 96 h after randomization, with greater weight loss [−2.5 vs. −1.5 kg; adjusted estimated difference (notionally 95% CI) −1.57 (−2.35 to −0.76); $P < 0.001$] but no significant differences in the VAS scores in patients assigned to HCTZ [mean AUC; 1500 (720–2610) vs. 1320 (330–2475); $P = 0.547$] (*Table 2*, *Figures 1* and *2A*). There was no significant difference between the two groups in the dyspnoea assessment using the Likert 7 scale either at 72 or 96 h (*Figure 2B*). At the time of discharge, the median (interquartile range) change in weight from randomization was greater in the HCTZ group compared with placebo [−2.95 (−5.40 to −1.52) vs.

Table 1 Characteristics of the patients at baseline

Characteristic	Placebo ($n = 116$)	Hydrochlorothiazide ($n = 114$)
Age (years)	82.0 (75.0–87.5)	83.0 (78.0–87.0)
Female sex	66 (56.9)	45 (39.5)
White race	116 (100)	113 (99.1)
Systolic blood pressure (mmHg)	130 (118–144)	121 (109–137)
Heart rate (bpm)	77 (66–89)	74 (68–85)
Baseline weight (kg)	79 (66–90)	77 (67–86)
Body mass index (kg/m^2)	33 (27–37)	30 (26–34)

Continued

Table 1 *Continued*

Characteristic	Placebo ($n = 116$)	Hydrochlorothiazide ($n = 114$)
Medical history		
Hypertension	102 (87.9)	103 (90.4)
Diabetes	66 (56.9)	64 (56.1)
Atrial fibrillation or flutter	73 (62.9)	85 (74.6)
Anaemia	53 (45.7)	50 (43.9)
Ischaemic cardiomyopathy	29 (25.2)	46 (40.4)
Pacemaker	26 (22.4)	23 (20.2)
Stroke	19 (16.4)	12 (10.5)
COPD	25 (21.6)	27 (23.7)
Congestion		
Rales	103 (88.8)	104 (91.2)
Edema	98 (84.5)	100 (87.7)
Pleural effusion	57 (49.1)	60 (52.6)
Ascites	9 (7.8)	15 (13.2)
Clinical features of heart failure		
NYHA functional class		
I	4 (3.4)	2 (1.7)
II	37 (31.9)	45 (39.8)
III	60 (51.7)	57 (50.4)
IV	15 (12.9)	9 (8.0)
LVEF (%)	57 (40–63)	55 (40–63)
HF-PEF (LVEF >50%)	75 (67.6)	68 (63.0)
Hospitalization for heart failure within previous 12 months	1 (0–2)	1 (0–2)
Emergency room visits for heart failure within previous 12 months	1 (0–2)	1 (0–3)
Analytical parameters		
Serum creatinine (μmoL/L)	122 (96–146)	128 (103–164)
Estimated GFR (mL/min/1.73 m^2)	43.5 (34.8–58.0)	43.0 (32.0–58.2)
Estimated GFR < 30 mL/min/1.73 m^2	18 (15.5)	23 (20.2)
Sodium (mmoL/L)	140 (137–142)	139 (136–142)
Potassium (mmoL/L)	4.20 (3.90–4.60)	4.37 (4.00–4.75)
Magnesium (mmoL/L)	2.0 (1.7–2.2)	2.1 (1.8–2.3)
BNP (pg/mL)	994 (376–1904)	1468 (565–3198)
NT-proBNP (pg/mL)	4330 (2301–9021)	4720 (2252–9000)
Medications		
ACE inhibitor or ARB	63 (54.3)	64 (56.2)
Beta-blocker	63 (54.3)	76 (66.7)
MRA (25 mg/day)	38 (32.8)	43 (37.7)
Oral furosemide dose (mg/day)	80 (80–100)	80 (80–120)

Values are given as *n* (%), or median (interquartile range).
ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; AUC, area under the curve; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; HF-PEF, heart failure with preserved ejection fraction; LVEF, left-ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; VAS, visual analogue scale.

Table 2 Primary, secondary, and safety endpoints

Endpoint	Placebo ($n = 116$)	Hydrochlorothiazide ($n = 114$)	*P*-value
Coprimary endpoints			
Change in weight at 72 h (kg)	−1.5 (−3.2 to 0.0)	−2.3 (−3.9 to −1.2)	0.002
Adjusted estimated difference (notionally 95% confidence interval)	−1.14 [−1.84 to −0.42]		
AUC for dyspnoea at 72 h (VAS)	720 (240–1455)	960 (360–1620)	0.497
Secondary endpoints			
Change in weight at 96 h (kg)	−1.5 (−3.5 to 0.0)	−2.5 (−4.5 to −1.4)	<0.001
Adjusted estimated difference (notionally 95% confidence interval)	−1.57 [−2.35 to −0.76]		
AUC for dyspnoea at 96 h (VAS)	1320 (330–2475)	1500 (720–2610)	0.547
Changes in patient-reported dyspnoea from baseline to 72 h (Likert 7)			
Worse	9 (7.8%)	3 (2.6%)	0.108
No change	26 (22.4%)	32 (28.1%)	
Better	81 (69.8%)	79 (69.3%)	
Changes in patient-reported dyspnoea from baseline to Day 5 (Likert 7)			
Worse	7 (6.0%)	7 (6.1%)	0.961
No change	23 (19.8%)	18 (15.8%)	
Better	86 (74.1%)	89 (78.1%)	
Metrics of diuretic response			
24 h diuresis quantification (mL)	1400 (1100–2162)	1775 (1212–2238)	0.05
Weight loss per 40 mg furosemide (from baseline to 72 h)	−0.2 (0.0 to −0.5)	−0.4 (−0.2 to −0.7)	<0.001
Weight loss per 40 mg furosemide (from baseline to 96 h)	−0.2 (0.0 to −0.5)	−0.4 (−0.2 to −0.6)	<0.001
Net fluid loss (mL) per 40 mg of furosemide	719 (461–1002)	787 (558–1098)	0.306
Mean loop diuretic dose administered from enrolment to 96 h	375 (299–480)	340 (262–475)	0.145
Hospital length of stay (days)	7.0 (6.0–12.5)	7.0 (5.0–9.0)	0.170
All-cause mortality at 30 days	7 (6.0%)	11 (9.6%)	0.438
All-cause mortality at 90 days	19 (16.4%)	23 (20.2%)	0.566
All-cause rehospitalizations at 30 days	19 (16.4%)	27 (23.7%)	0.223
All-cause rehospitalizations at 90 days	40 (34.5%)	43 (37.7%)	0.709
Safety endpoints			
Impaired renal function*	20 (17.2%)	53 (46.5%)	<0.001
Increase in creatinine > 26.5 μmol/L	20 (17.2%)	53 (46.5%)	<0.001
Decrease in eGFR > 50%	1 (0.9%)	1 (0.9%)	1.000
Changes in sodium levels (hyponatraemia)			
Sodium level ≤ 130 mmoL/L	6 (5.2%)	10 (8.8%)	0.416
Sodium level ≤ 125 mmoL/L	2 (1.7%)	3 (2.6%)	0.682
Changes in potassium levels (hypokalaemia)			
Potassium levels ≤ 3.5 mmoL/L	22 (19.0%)	51 (44.7%)	<0.001
Potassium levels ≤ 3.0 mmoL/L	18 (16.1%)	43 (40.6%)	<0.001
Potassium levels ≤ 2.5 mmoL/L	0 (0.0%)	2 (1.8%)	0.245

*Impaired renal function was defined as an increase in either serum creatinine levels >26.5 μmoL/L or a decrease in serum eGFR higher than 50% both in reference to their levels at baseline.
AUC, area under the curve; eGFR, estimated glomerular filtration rate; VAS, visual analogue scale.

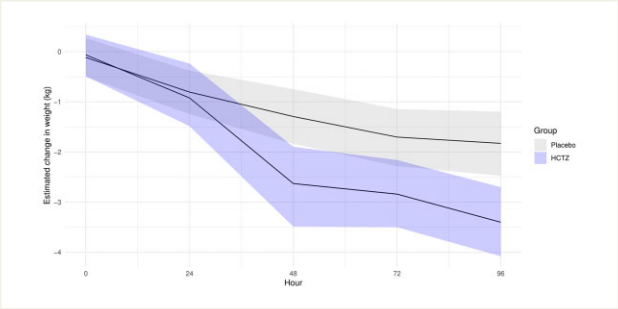


Figure 1 Adjusted changes in weight (kg) from randomization to 72 and 96 h and in the hydrochlorothiazide and placebo groups. Estimated mean change throughout daily visits (black line) by group and cases bootstrap confidence intervals (shadowed bands)

−2.20 [−5.82 to −0.60)], but this difference was not statistically significant ($P = 0.261$). The effect of HCTZ on the primary endpoint was generally consistent across different subgroups (*Figure 3* and Supplementary material online, *Figure S2*).

Regarding the metric of the diuretic response, patients allocated to HCTZ showed significantly greater 24 h diuresis (1775 vs. 1400 mL; $P = 0.05$) and weight loss for each 40 mg of furosemide (both at 72 and 96 h) ($P < 0.001$) (*Figure 4*) but there were no significant differences in net fluid loss per milligram of furosemide (787 vs. 719 mL; $P = 0.306$). The total mean loop diuretic dose administered from enrolment to 72 h was 375 mg in the placebo group and 340 mg in the HCTZ group ($P = 0.145$). The dose of loop diuretic was reduced in a significantly higher proportion of patients in the HCTZ group at the end of the study treatment period [34 (31.5%) vs. 19 (17.4%); $P = 0.045$]. There was no significant difference in the likelihood of a switch to oral diuretics during the study treatment period and until hospital discharge [35 (33%) in the placebo group and 38 (36%) in the HCTZ group, $P = 0.832$]. Diuretic treatment at baseline, during the treatment period, at discharge and during the follow-up period is detailed in Supplementary material online, *Table S2*.

In relation to clinical congestion, we have carried out a post-hoc exploratory analysis of congestion variables, finding that at 72 and 96 h after randomization patients assigned to HCTZ had fewer, peripheral edema, pleural effusion, and ascites compared with those assigned to placebo (see Supplementary material online, *Figure S3*).

Ninety-six hours after randomization, the median (IQR) natriuresis was 64 mmoL/L (42–92) in the HCTZ group and 47 mmoL/L (26–81) in the placebo group ($P = 0.004$), but there were no differences in the median change in urinary sodium from randomization to 96 h between the two groups (16.5 vs. 14.5 mmoL; $P = 0.842$).

The median length of stay during the index hospitalization was 7 days and did not differ significantly across the treatment groups. A total of 42 patients (18.3%) died and 83 (36.1%) were rehospitalized within the 90-day follow-up period, but there were no significant differences between groups in mortality (19 events and 23 events, respectively; hazard ratio 1.26; 95% CI: 0.68–2.34; $P = 0.46$) or rehospitalizations (40 events and 43 events, respectively; hazard ratio 1.25; 95% CI: 0.81–1.93; $P = 0.32$) (*Figures 5* and *6*). When we analyse mortality or rehospitalization as a post-hoc combined endpoint (90-day mortality or rehospitalization), we also found no significant differences between the two groups (hazard ratio 1.25; 95% CI: 0.81 to 1.92; $P = 0.32$). The competing risk results show that there were no statistically significant differences in the cumulative incidence function for hospital readmission (Fine–Gray estimated coefficient 1.22, 95% CI: 0.8–1.88; $P = 0.36$) (see Supplementary material online, *Figure S4*).

Clinical events and safety

A higher proportion of patients who received HCTZ met the prespecified safety endpoint of impaired renal function which occurred in 53 (46.5%) patients when compared with 20 (17.2%) patients in the placebo group ($P < 0.001$). The median increase in serum creatinine level at 5 days was 0.00 (10.6–18.6) µmoL/L with placebo and 15.9 (7.1–37.1) µmoL/L with HCTZ; $P < 0.001$. Only one patient (assigned to the placebo arm) received renal replacement therapy (haemodialysis). There were no significant differences between these two treatment groups in the other safety endpoints, hyponatraemia, and hypokalaemia. However, in a post-hoc analysis using higher potassium cut-off points (≤3.5 and ≤3.0 mmoL/L), hypokalaemia was more frequent in those who received HCTZ. The median maximum decrease in serum potassium levels from baseline to hospital discharge was −0.36 (95% CI: −0.46 to −0.26) with placebo and −0.70 (95% CI: −0.81 to −0.60) with HCTZ, providing a significant difference of −0.33 (95% CI: −0.50 to −0.20) between groups. The median maximum decrease in serum sodium levels was −2.6 (95% CI: −3.5 to −2.0) with placebo and −3.4 (95% CI: −4.0 to −2.5) with HCTZ, providing a non-significant difference of −0.7 (95% CI: −1.5 to 0.2) between groups. In addition, hyperkalaemia (defined as potassium levels >5.0 mmoL/L) was similar between the two groups [26 (22.4%) and 25 (21.9%) in those assigned to placebo and HCTZ, respectively]. In relation to magnesium, there were no differences in magnesium values at baseline or at discharge, and there were no cases of hypomagnesaemia.

There were no differences between HCTZ and placebo in the proportion of patients with serious adverse events reported by the investigators (23% in each group, $P = 0.93$). Individual rates of adverse events are shown in the Supplementary material online, *Table S3*. Serious cardiac events were similar in the two groups (11 vs. 8). Renal failure and hyperkalaemia were more frequent with placebo (5 vs. 2 and 2 vs. 0, respectively), but hyponatraemia was more frequent with HCTZ (1 vs. 3). Other miscellaneous types of adverse events were more frequently reported among patients receiving HCTZ. No symptomatic hypotension was reported as a serious adverse event and the proportion of patients that presented asymptomatic hypotension (systolic blood pressure lower than 90 mmHg) was similar in both treatment groups; 10 (8.7%) and 11 (9.9%) in those assigned to placebo and HCTZ, respectively.

Discussion

In this clinical trial of patients with acute decompensated HF and persistent congestion adding oral HCTZ to intravenous furosemide improved the diuretic response. There was a benefit for most of the primary or secondary endpoints, including changes in weight, urine output and metrics of diuretic response, although only weight differences and weight differences per mg of furosemide were statistically significant (*Structured Graphical Abstract*).

This study is the first double-blind, randomized, multicentre clinical trial assessing the efficacy and safety of HCTZ in AHF. Our findings are consistent with prior observational studies (and one small randomized trial) suggesting that diuretic therapy combining any of several thiazide diuretics can increase urine excretion and induce weight loss and oedema resolution.[4,12–14]

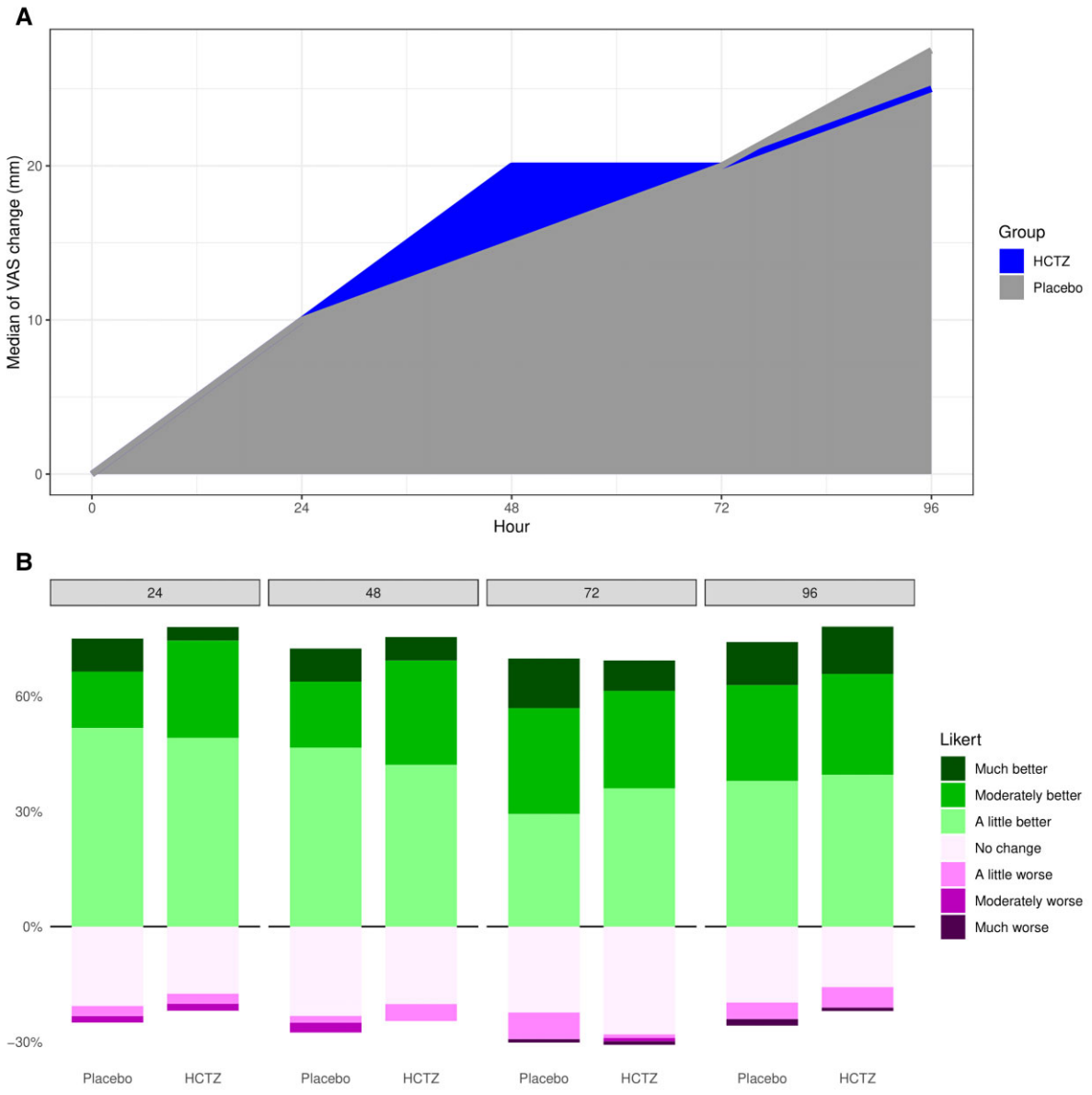


Figure 2 Patient-reported change in dyspnoea. (*A*) Measured as the mean area under the curve of daily visual analogue scale assessments by treatment group from randomization and until 72 and 96 h, where increasing values represent improvements in dyspnoea. (*B*) Measured daily with a seven-level Likert scale in each treatment group, where improvement, even minimal, is highlighted in positive in vertical axis

We found no significant differences in patients' global assessment of symptoms using dyspnoea scales and this finding is consistent with those of other clinical trials. Patient-assessed dyspnoea is modestly correlated with more objective physician-assessed changes in signs of HF, such as jugular venous distention and peripheral oedema, or physician-assessed New York Heart Association class. Although it is often assumed that dyspnoea will resolve quickly with standard treatment, it has been suggested that moderate or severe dyspnoea persists beyond the initial treatment phase in many patients with AHF.[5,15]

Worsening renal function occurs frequently in patients with AHF and has been classically related with greater morbidity and mortality.[16] Although worsening of renal function occurred more frequently with HCTZ, there was no short-term evidence of worse clinical outcomes between the two groups at 90 days. This observation is consistent with more contemporary research interpreting worsening renal function in the context of decongestion in AHF that suggests that the association between worsening renal function and clinical outcomes depends on diuretic response.[17]

There is a substantial concern about the risk of adverse events with the use of thiazides combined with loop diuretics in patients with HF. This concern is mainly based on a retrospective observational analysis employing propensity matching, showing that the combination diuretic therapy with metolazone (the most widely used thiazide-like diuretic in the USA) was associated with an increased risk of hypokalaemia, hyponatraemia, worsening renal function, and mortality.[18,19] In contrast, in this trial, we did not observe a significant risk of hyponatraemia, hypokalaemia, or mortality.

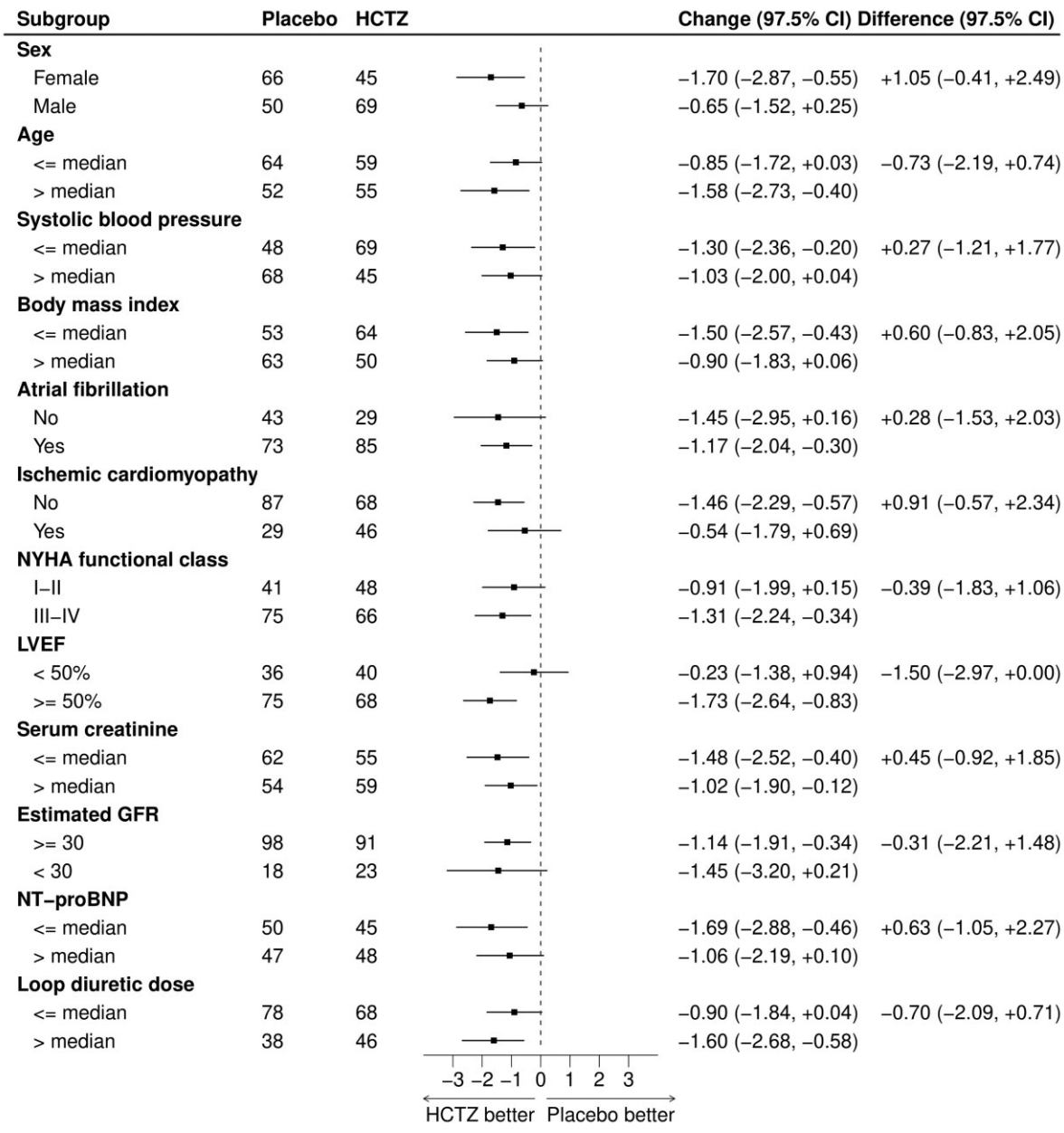


Figure 3 Subgroup analysis. Subgroups that were defined according to quantitative variables were based on observed median values at randomization

Hypotension is another concern associated with combined diuretic therapy[4] but, in this trial, even though the HCTZ group had lower baseline systolic blood pressure values, there was no increased risk of hypotension.

There is an old belief that thiazides lack efficacy in patients with glomerular filtration rate <30 mL/min. This notion is based on a small study in which chlorothiazide was administered at a dose of 500 mg intravenously in 12 patients with a wide range of glomerular filtration rate but who had no oedema and no HF. Two patients with the lowest glomerular filtration rates (11 and 6.3 mL/min) had a minimal natriuretic response.[20] Nevertheless, more recent studies have shown that combined regimens are more potent than HCTZ or furosemide in monotherapy for increasing fractional excretions of sodium and chloride in patients with hypertension and Stage 4 or 5 chronic kidney disease,[21] and that the use of chlorthalidone therapy in patients with advanced chronic kidney disease and poorly controlled hypertension can improve blood pressure control.[22] Diuretic efficacy is a function of drug delivery to the site of action, so higher doses are required in the face of severe renal dysfunction.

There were no differences in the length of hospital stay despite a better diuretic response with HCTZ. This may be explained, in part, because all patients had to be admitted (and could not be discharged) during the 5-day randomized treatment period for close monitoring of adverse effects.

The strength of this trial is that eligibility criteria were chosen to select a cohort generalizable to the AHF population with diuretic resistance. The admission due to AHF decompensation despite being treated with 80 mg or more of loop diuretics and the low urinary natriuresis highly suggest this fact.

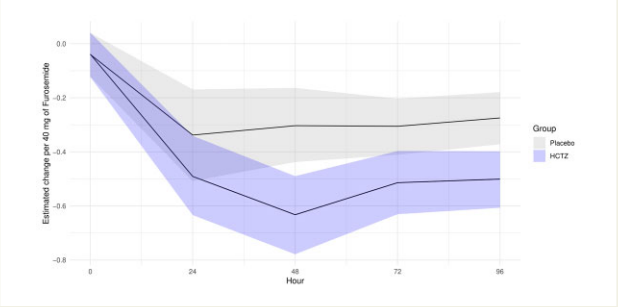


Figure 4 Adjusted changes in weight (kg) per 40 mg of furosemide from randomization to 72 and 96 h in the hydrochlorothiazide and placebo groups. Estimated mean change throughout daily visits (black line) by group and cases bootstrap 95% confidence intervals (shadowed bands)

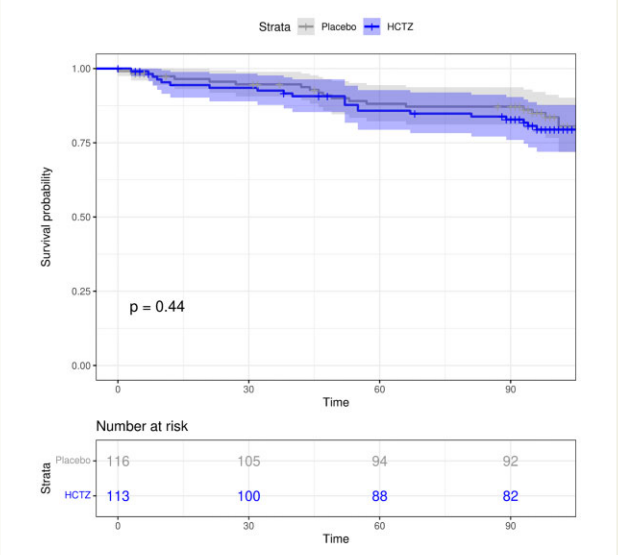


Figure 5 Comparative survival analysis for all-cause mortality during the 90-day follow-up period stratified by treatment group according to the Kaplan–Meier method, using the log-rank test for comparison

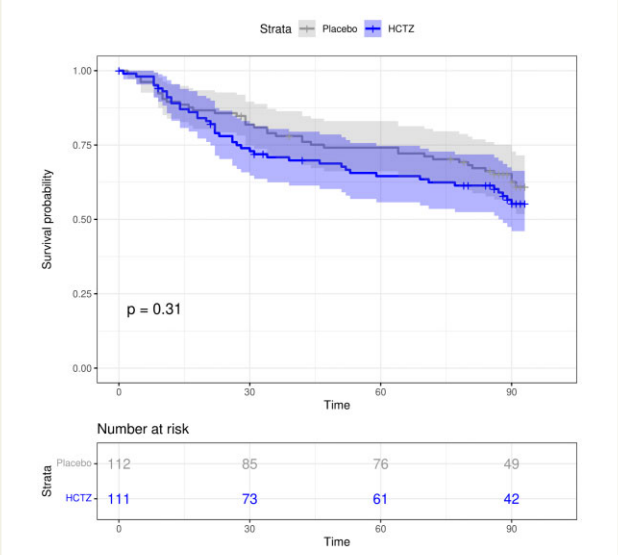


Figure 6 Comparative survival analysis for readmission during the 90-day follow-up period stratified by treatment group according to the Kaplan–Meier method, using the log-rank test for comparison

The results of this study are consistent with those of the recently reported ADVOR trial, which found that the addition of acetazolamide to intravenous loop diuretic therapy in patients with AHF resulted in a greater incidence of successful decongestion.[23] It is important to note that, in this trial, the patients who were receiving a higher maintenance dose of oral loop diuretics had less benefit than those who were receiving a lower maintenance dose.

This study has several limitations. First, recruitment did not reach the post size required by the protocol due to slow enrolment. The main reasons for this slow enrolment were the following: (i) more than 70% of patients admitted for AHF were on baseline doses of furosemide lower than 80 mg/day (or did not received loop diuretics during the previous month); (ii) logistical problems to recruit patients within the first 24 h after hospital admission was the main reason in some centres; (iii) cognitive impairment made difficult to correctly assess the dyspnoea scales; and (iv) life expectancy of <6 months due to other comorbidities. Other less frequent but also important reasons were refusal to obtain informed consent and receiving baseline treatment with thiazides. However, given that the mean and standard deviation of weight loss at 72 h were much smaller (2.9 kg) than those assumed for the sample size calculation (4.5 kg), a post-hoc power estimation with a Type I error of 0.025 (since there were two primary outcomes) provided a power of 81%. Despite the difficulties in recruiting and the time invested to carry out this trial, the evidence provided is greater than that of observational studies, no matter how large they may be. Efforts should be directed towards carrying out this type of independent and multicentre trials with international collaboration and with greater funding to overcome these limitations. Second, four characteristics of the patients at baseline were unbalanced between the two treatment groups, including gender, systolic blood pressure, body mass index, and ischaemic cause of HF. Third, we observed a large relative but small absolute overall weight loss and, as there was no specific requirement for congestion at inclusion, maybe if more volume overloaded patients had been enrolled, we would have seen larger absolute reductions in weight. Forth, the patients who participated in the trial had a history of chronic HF and required moderate-to-high doses of loop diuretics before admission (which is the case for 20–30% of patients with chronic HF who are admitted due to decompensation).[24,25] Our findings may not be applicable to patients with newly diagnosed HF or those with more modest diuretic requirements. Finally, in the follow-up visits, neither renal function nor electrolytes were monitored, so we cannot guarantee that the worsening of renal function is transient and associated with a good diuretic response.

In conclusion, adding oral HCTZ to intravenous furosemide is an adequate strategy to improve diuretic response in patients with acute decompensated HF.

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Supplementary data

Supplementary data are available at *European Heart Journal* online.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Conflict of interest: All authors declare no conflict of interest for this contribution.

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