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

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Abstract

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 kg; adjusted estimated difference (notionally 95% confidence interval) −1.14 (−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 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

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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. 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. 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.

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
Combing loop with thiazide diuretics

sodium absorption in the case of (prolonged) loop diuretic administration. 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. Moreover, in view of the relative safety of high-dose loop diuretics in the DOSE-AHF trial, expert recommendations have given preference to initial intensification of the loop diuretic dose before adding a thiazide diuretic.

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 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.

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 lower than 2.5 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 randomisation code 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. 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) 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·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 χ² 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. Interaction with group and time was examined. 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 dyspnoea VAS scores changes from baseline throughout the study 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 m²), 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; 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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n = 116)</th>
<th>Hydrochlorothiazide (n = 114)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>82.0 (75.0–87.5)</td>
<td>83.0 (78.0–87.0)</td>
</tr>
<tr>
<td>Female sex</td>
<td>66 (56.9)</td>
<td>45 (39.5)</td>
</tr>
<tr>
<td>White race</td>
<td>116 (100)</td>
<td>113 (99.1)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>130 (118–144)</td>
<td>121 (109–137)</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>77 (66–89)</td>
<td>74 (68–85)</td>
</tr>
<tr>
<td>Baseline weight (kg)</td>
<td>79 (66–90)</td>
<td>77 (67–86)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>33 (27–37)</td>
<td>30 (26–34)</td>
</tr>
</tbody>
</table>

Continued
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n = 116)</th>
<th>Hydrochlorothiazide (n = 114)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical history</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>102 (87.9)</td>
<td>103 (90.4)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>66 (56.9)</td>
<td>64 (56.1)</td>
</tr>
<tr>
<td>Atrial fibrillation or flutter</td>
<td>73 (62.9)</td>
<td>85 (74.6)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>53 (45.7)</td>
<td>50 (43.9)</td>
</tr>
<tr>
<td>Ischaemic cardiomyopathy</td>
<td>29 (25.2)</td>
<td>46 (40.4)</td>
</tr>
<tr>
<td>Pacemaker</td>
<td>26 (22.4)</td>
<td>23 (20.2)</td>
</tr>
<tr>
<td>Stroke</td>
<td>19 (16.4)</td>
<td>12 (10.5)</td>
</tr>
<tr>
<td>COPD</td>
<td>25 (21.6)</td>
<td>27 (23.7)</td>
</tr>
<tr>
<td><strong>Congestion</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rales</td>
<td>103 (88.8)</td>
<td>104 (91.2)</td>
</tr>
<tr>
<td>Edema</td>
<td>98 (84.5)</td>
<td>100 (87.7)</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>57 (49.1)</td>
<td>60 (52.6)</td>
</tr>
<tr>
<td>Ascites</td>
<td>9 (7.8)</td>
<td>15 (13.2)</td>
</tr>
<tr>
<td><strong>Clinical features of heart failure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA functional class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>4 (3.4)</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>II</td>
<td>37 (31.9)</td>
<td>45 (39.8)</td>
</tr>
<tr>
<td>III</td>
<td>60 (51.7)</td>
<td>57 (50.4)</td>
</tr>
<tr>
<td>IV</td>
<td>15 (12.9)</td>
<td>9 (8.0)</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>57 (40–63)</td>
<td>55 (40–63)</td>
</tr>
<tr>
<td>HF-PEF (LVEF &gt;50%)</td>
<td>75 (67.6)</td>
<td>68 (63.0)</td>
</tr>
<tr>
<td>Hospitalization for heart failure within previous 12 months</td>
<td>1 (0–2)</td>
<td>1 (0–2)</td>
</tr>
<tr>
<td>Emergency room visits for heart failure within previous 12 months</td>
<td>1 (0–2)</td>
<td>1 (0–3)</td>
</tr>
<tr>
<td><strong>Analytical parameters</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine (μmol/L)</td>
<td>122 (96–146)</td>
<td>128 (103–164)</td>
</tr>
<tr>
<td>Estimated GFR (mL/min/1.73 m²)</td>
<td>43.5 (34.8–58.0)</td>
<td>43.0 (32.0–58.2)</td>
</tr>
<tr>
<td>Estimated GFR &lt; 30 mL/min/1.73 m²</td>
<td>18 (15.3)</td>
<td>23 (20.2)</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>140 (137–142)</td>
<td>139 (136–142)</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>4.20 (3.90–4.60)</td>
<td>4.37 (4.00–4.75)</td>
</tr>
<tr>
<td>Magnesium (mmol/L)</td>
<td>2.0 (1.7–2.2)</td>
<td>2.1 (1.8–2.3)</td>
</tr>
<tr>
<td>BNP (pg/mL)</td>
<td>994 (376–1904)</td>
<td>1468 (356–3198)</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL)</td>
<td>4330 (2301–9021)</td>
<td>4720 (2252–9000)</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>63 (54.3)</td>
<td>64 (56.2)</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>63 (54.3)</td>
<td>76 (66.7)</td>
</tr>
<tr>
<td>MRA (25 mg/day)</td>
<td>38 (32.8)</td>
<td>43 (37.7)</td>
</tr>
<tr>
<td>Oral furosemide dose (mg/day)</td>
<td>80 (80–100)</td>
<td>80 (80–120)</td>
</tr>
</tbody>
</table>

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

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

*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.
Clinical events and safety

A higher proportion of patients who received HCTZ met the pre-specified 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, hypotriatremia, 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 hypotriatremia 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 who 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 decompenated 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
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.
Hypotension is another concern associated with combined diuretic therapy 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. 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, and that the use of chlorthalidone therapy in patients with advanced chronic kidney disease and poorly controlled hypertension can improve blood pressure control. 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.

**Table 1** Subgroup analysis. Subgroups that were defined according to quantitative variables were based on observed median values at randomization.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Placebo</th>
<th>HCTZ</th>
<th>Change (97.5% CI)</th>
<th>Difference (97.5% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>66</td>
<td>45</td>
<td>-1.70 (-2.87, -0.55)</td>
<td>1.05 (-0.41, 2.49)</td>
</tr>
<tr>
<td>Male</td>
<td>50</td>
<td>69</td>
<td>-0.65 (-1.52, +0.25)</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;= median</td>
<td>64</td>
<td>59</td>
<td>-0.85 (-1.72, +0.03)</td>
<td>-0.73 (-2.19, +0.74)</td>
</tr>
<tr>
<td>&gt; median</td>
<td>52</td>
<td>55</td>
<td>-1.58 (-2.73, -0.40)</td>
<td></td>
</tr>
<tr>
<td><strong>Systolic blood pressure</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>&lt;= median</td>
<td>48</td>
<td>69</td>
<td>-1.30 (-2.36, -0.20)</td>
<td>0.27 (-1.21, +1.77)</td>
</tr>
<tr>
<td>&gt; median</td>
<td>66</td>
<td>45</td>
<td>-1.03 (-2.00, +0.04)</td>
<td></td>
</tr>
<tr>
<td><strong>Body mass index</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;= median</td>
<td>53</td>
<td>64</td>
<td>-1.50 (-2.57, -0.43)</td>
<td>0.60 (-0.83, +2.05)</td>
</tr>
<tr>
<td>&gt; median</td>
<td>63</td>
<td>50</td>
<td>-0.90 (-1.83, -0.06)</td>
<td></td>
</tr>
<tr>
<td><strong>Atrial fibrillation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>43</td>
<td>29</td>
<td>-1.45 (-2.95, +0.16)</td>
<td>0.28 (-1.53, +2.03)</td>
</tr>
<tr>
<td>Yes</td>
<td>73</td>
<td>85</td>
<td>-1.17 (-2.04, -0.30)</td>
<td></td>
</tr>
<tr>
<td><strong>Ischemic cardiomyopathy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>87</td>
<td>68</td>
<td>-1.46 (-2.29, -0.57)</td>
<td>0.91 (-0.57, +2.34)</td>
</tr>
<tr>
<td>Yes</td>
<td>29</td>
<td>46</td>
<td>-0.54 (-1.79, +0.69)</td>
<td></td>
</tr>
<tr>
<td><strong>NYHA functional class</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>I–II</td>
<td>41</td>
<td>48</td>
<td>-0.91 (-1.99, +0.15)</td>
<td>-0.39 (-1.83, +1.06)</td>
</tr>
<tr>
<td>III–IV</td>
<td>75</td>
<td>66</td>
<td>-1.31 (-2.24, -0.34)</td>
<td></td>
</tr>
<tr>
<td><strong>LVEF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 50%</td>
<td>36</td>
<td>40</td>
<td>-0.23 (-1.38, +0.94)</td>
<td>-1.50 (-2.37, +0.00)</td>
</tr>
<tr>
<td>&gt;= 50%</td>
<td>75</td>
<td>68</td>
<td>-1.73 (-2.64, -0.83)</td>
<td></td>
</tr>
<tr>
<td><strong>Serum creatinine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;= median</td>
<td>62</td>
<td>55</td>
<td>-1.48 (-2.52, -0.40)</td>
<td>0.45 (-0.92, +1.85)</td>
</tr>
<tr>
<td>&gt; median</td>
<td>54</td>
<td>59</td>
<td>-1.02 (-1.90, -0.12)</td>
<td></td>
</tr>
<tr>
<td><strong>Estimated GFR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;= 30</td>
<td>98</td>
<td>91</td>
<td>-1.14 (-1.91, -0.34)</td>
<td>-0.31 (-2.21, +1.48)</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>18</td>
<td>23</td>
<td>-1.45 (-3.20, +0.21)</td>
<td></td>
</tr>
<tr>
<td><strong>NT-proBNP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;= median</td>
<td>50</td>
<td>45</td>
<td>-1.69 (-2.88, -0.46)</td>
<td>0.63 (-1.05, +2.27)</td>
</tr>
<tr>
<td>&gt; median</td>
<td>47</td>
<td>48</td>
<td>-1.06 (-2.19, +0.10)</td>
<td></td>
</tr>
<tr>
<td><strong>Loop diuretic dose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;= median</td>
<td>78</td>
<td>68</td>
<td>-0.90 (-1.84, +0.04)</td>
<td>-0.70 (-2.09, +0.71)</td>
</tr>
<tr>
<td>&gt; median</td>
<td>38</td>
<td>46</td>
<td>-1.60 (-2.68, -0.58)</td>
<td></td>
</tr>
</tbody>
</table>

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

Trial numbers: Clinicaltrials.gov: NCT01647932; EudraCT Number: 2013-001852-36

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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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References