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RESEARCH ARTICLE

Combining loop and thiazide diuretics for acute heart failure across the estimated glomerular filtration rate spectrum: A post-hoc analysis of the CLOROTIC trial

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Aims In patients with acute heart failure (AHF), the addition of hydrochlorothiazide (HCTZ) to furosemide improved diuretic response in the CLOROTIC trial. This work aimed to evaluate if these effects differ across the estimated glomerular filtration rate (eGFR) spectrum.

Methods and results This post-hoc analysis of the CLOROTIC trial analysed 230 patients with AHF and explored the influence of eGFR on primary and secondary endpoints. The median eGFR was 43 ml/min/1.73 m^2 (range 14–109) and 23% had eGFR ≥60 ml/min/1.73 m^2 (group 1), 24% from 45 to 59 ml/min/1.73 m^2 (group 2), and 53% <45 ml/min/1.73 m^2 (group 3). Patients treated with HCTZ had greatest weight loss at 72 h in all three groups, but patients in group 1 had a significantly greater response (−2.1 kg [−3.0 to 0.5]), compared to patients in groups 2 (−1.3 kg [−2.3 to 0.2]) and 3 (−0.1 kg [−1.3 to 0.4]) (*p*-value for interaction = 0.246). At 96 h, the differences in weight were −1.8 kg (−3.0 to −0.3), −1.4 kg (−2.6 to 0.3), and −0.5 kg (−1.3 to −0.1) in groups 1, 2, and 3, respectively (*p*-value for interaction = 0.256). There were no significant differences observed with the addition of HCTZ in terms of diuretic response, mortality or rehospitalizations, or safety endpoints (impaired renal function, hyponatraemia, and hypokalaemia) among the three eGFR groups (all *p*-values for interaction were no significant).

Conclusion The addition of eGFR-adjusted doses of oral HCTZ to loop diuretics in patients with AHF improved diuretic response across the eGFR spectrum.
Clinical Trial Registration: ClinicalTrials.gov: NCT01647932; EudraCT number: 2013–001852-36.

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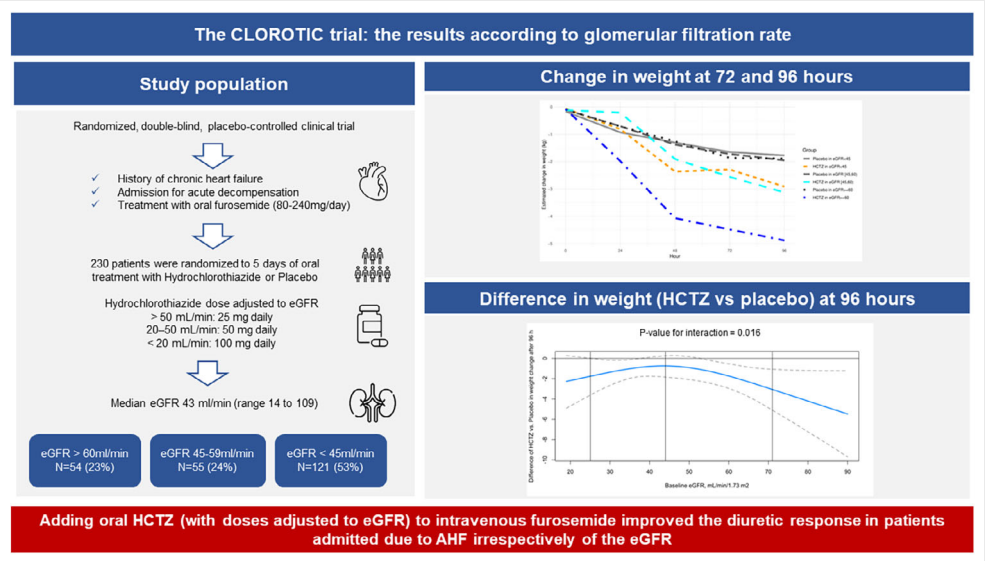
Graphical Abstract



Results of the CLOROTIC trial according to glomerular filtration rate. AHF, acute heart failure; eGFR, estimated glomerular filtration rate; HCTZ, hydrochlorothiazide.

Keywords Heart failure • Glomerular filtration rate • Diuretics • Thiazides • Furosemide

Introduction

The Combination of Loop With Thiazide-type Diuretics in Patients With Decompensated Heart Failure (CLOROTIC) trial evaluated the effect of adding oral hydrochlorothiazide (HCTZ) to intravenous furosemide on diuretic response in patients admitted for acute heart failure (AHF) who were already receiving prior baseline treatment of at least 80 mg of oral furosemide or an equivalent dose of torsemide.[1,2] The CLOROTIC trial provided relevant new information, showing that the addition of HCTZ to intravenous furosemide improved diuretic response in these patients.[1] Resistance to loop diuretic therapy may develop as a result of hypertrophy of the distal nephron segments and a subsequent increase in sodium reabsorption. Adding a thiazide diuretic may help overcome this effect by blocking distal tubule sodium reabsorption.[3] Indeed, the current European Society of Cardiology (ESC) guidelines on the diagnosis and treatment of AHF state that the combination of a loop diuretic with a thiazide diuretic should be considered in patients with resistant oedema who do not respond to an increase in loop diuretic dose (recommendation class IIa, level of evidence B).[4] Previously, it was commonly thought that thiazides lacked diuretic efficacy when the estimated glomerular filtration rate (eGFR) is below 30 ml/min/1.73 m^2,[5] but more recent evidence suggests a clear effect of thiazides, especially in patients with poor renal function.[6] However, their diuretic efficacy is based on drug delivery to the site of action and, thus, higher doses may be required when severe renal dysfunction is also present. Therefore, increasing the thiazide diuretic dose as the eGFR declines, as was done in the CLOROTIC trial with HCTZ, might be an effective approach for increasing fluid loss.[1,2,7]

This study is a post-hoc analysis of the CLOROTIC trial and aims to assess the diuretic response to HCTZ across the eGFR spectrum. To do so, the influence of baseline eGFR on the primary and secondary endpoints (changes in body weight at 72 and 96 h after randomization, metrics of diuretic response, and mortality/rehospitalizations during the follow-up period) and safety endpoints were analysed.

Methods

Trial design and participants

The CLOROTIC study was a multicentre, prospective, randomized, double-blind, placebo-controlled trial that was designed, conducted, and funded by the Heart Failure Working Group of the Spanish Society of Internal Medicine. More information on the design and main results of the trial have previously been published.[1,2] Briefly, all patients 18 years or older with a prior history of chronic heart

failure (HF) and a hospital admission due to AHF were eligible for participation. In addition, oral maintenance therapy with at least 80 mg of furosemide (or an equivalent dose of a different loop diuretic) for at least 1 month prior to the index admission was also an inclusion criterion. Patients were excluded if they were clinically unstable on admission (acute coronary syndrome, cardiogenic shock, or need for intensive care unit management) or had been treated with inotropic agents or any thiazide diuretic during the month before admission (prior use of mineralocorticoid receptor antagonists was not considered an exclusion criterion if the patient had been receiving them on a long-term basis). The eGFR values upon admission were not an exclusion criterion except if the patient was on or required renal replacement therapy. Hypokalaemia and hyponatraemia were exclusion criteria if potassium or sodium values at randomization were equal to or less than 2.5 mmol/L and 125 mmol/L, respectively.

The study was approved by the Spanish Agency of Medicines and Medical Products (AEMPS, for its initials in Spanish) and the local institutional ethics committees at each site. All patients provided written informed consent.

Trial intervention

Patients were randomly assigned in a 1:1 ratio within the first 24 h after hospital admission to receive oral tablets of either HCTZ or a placebo for 5 days. Oral HCTZ doses were adjusted according to three eGFR categories, calculated using the Modification of Diet in Renal Disease formula, which were as follows: >50 ml/min/1.73 m^2, 25 mg once daily; 20–50 ml/min/1.73 m^2, 50 mg once daily; and <20 ml/min/1.73 m^2, 100 mg once daily. Patients received the same HCTZ dose during the treatment period; up-titration or down-titration was not permitted. However, the dose of HCTZ could be adjusted based on changes in eGFR category observed during the intervention period. To ensure identical intravenous loop diuretic administration in all participating centres, an algorithm for furosemide dosage was recommended. All patients were monitored during the intervention period until hospital discharge and then for an additional safety follow-up period of 90 days after discharge.[1,2]

Endpoints

The primary efficacy endpoints were changes in body weight and changes in patient-reported dyspnoea from baseline to 72 h after randomization. The pre-defined secondary endpoints included the following: changes in body weight and patient-reported dyspnoea at 96 h after randomization, metrics of diuretic response, length of hospital stay, and mortality and rehospitalizations at 30 and 90 days. The metrics of diuretic response included 24-h urine volume, weight loss per 40 mg of furosemide (at 72 and 96 h), net fluid loss (24-h urine volume) per milligram of furosemide, and mean loop diuretic dose administered from the time of enrolment up to 72 h. 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 to >26.5 μmol/L or a decrease in eGFR ≥50% compared to the value upon admission. Hypokalaemia and hyponatraemia were defined as potassium levels ≤2.5 mmol/L and sodium levels ≤125 mmol/L, respectively. A post-hoc analysis using higher (less severe) cut-off values was also conducted (sodium ≤130 mmol/L and potassium ≤3.5 and ≤3.0 mmol/L).

Renal function according to estimated glomerular filtration rate

This study evaluated whether renal function at the time of randomization had an influence on the trial's primary, secondary, and safety outcomes. This post-hoc analysis was conducted on three eGFR categories: ≥60 ml/min/1.73 m^2 (group 1), 45–59 ml/min/1.73 m^2 (group 2), and <45 ml/min/1.73 m^2 (group 3). An analysis was also performed on eGFR as a continuous variable.

Statistical analysis

Summary measures of median (interquartile range [IQR]) and absolute (relative) frequencies were used for the quantitative and qualitative variables, respectively. Quantitative variables and their changes from baseline were compared among groups using the Kruskal–Wallis test. Qualitative variables were compared among groups using Pearson's chi-squared test (or Fisher's exact test if expected frequencies were <5).

The possible interaction of HCTZ with eGFR groups was assessed for all the primary, secondary and safety outcomes by applying regression models. The safety endpoints included any event observed at any time throughout the study. The regression models included a quantile regression model for the median change from baseline, Cox proportional hazards models for survival outcomes, and a logistic regression model for binary outcomes. All were adjusted according to weight at baseline and the set of unbalanced variables between HCTZ and placebo at baseline.

The *p*-value of the interaction between the randomly allocated treatment and eGFR groups was assessed by comparing the model including both main effects and their interaction with the model only including both main effects and all the variables of adjustment with no interaction. Specifically, the ANOVA function with rank test and normal score was used for quantile regression models and the analysis of deviance chi-square test was used for both Cox proportional hazards and logistic regression models. If non-significant, the *p*-value for the eGFR groups main effect (obtained by comparing the model with and without it) was estimated. The possible interaction of HCTZ with eGFR values (in continuum) was assessed using regression models with restricted cubic splines applied to eGFR (without assuming a linear trend) with three knots located at the 10th, 50th, and 90th percentiles. These regression models included linear, logistic, and Cox proportional hazard models for quantitative, binary, and survival outcomes, respectively, and adjusted by the weight at baseline and the set of unbalanced variables at baseline. Mean changes from randomization and throughout the intervention period in weight loss and in weight loss per 40 mg of furosemide were represented graphically. They were estimated by linear mixed-effects models with the random effect of patient and the fixed effects of the weight at baseline and the interaction between eGFR level, group, and time. No form of trend was assumed for time, it was introduced as a qualitative variable into the models. The identified unbalanced variables between the randomized groups at baseline were added to the mixed-effects models to subtract their possible effect from the treatment effect estimation. Non-parametric cases bootstrap 97.5% confidence interval (CI) based on 5000 replicates (resampling patients) was added to the mean estimates in each figure based on mixed-effects models.

All statistical analyses were performed in R, applying a significance level of 0.025 (and therefore having a 97.5% CI, 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 230 patients were enrolled in the CLOROTIC trial. The mean age was 83 years and 48% were female. Median (IQR) eGFR was 43 (35–58) ml/min/1.73 m^2 and ranged from 14 to 109 ml/min/1.73 m^2. Fifty-four (23%) patients had an eGFR ≥60 ml/min/1.73 m^2 (group 1), 55 (24%) had an eGFR of 45–59 ml/min/1.73 m^2 (group 2), and 121 (53%) had an eGFR <45 ml/min/1.73 m^2 (group 3). The proportion of patients receiving HCTZ or the placebo was balanced among the three groups.

The baseline characteristics of the patients and comparisons according to the three eGFR categories are shown in *Table 1*. Patients with the lowest admission eGFR value (group 3) had more anaemia and higher serum potassium and N-terminal pro-B-type natriuretic peptide values at baseline and received less treatment with renin–angiotensin system inhibitors and mineralocorticoid receptor antagonists. Patients in group 2 had the highest baseline weight and body mass index values. There were no differences in the median dose of oral furosemide at baseline among the three groups.

Effect of estimated glomerular filtration rate on the treatment effect for primary and secondary efficacy endpoints

The results on primary and secondary efficacy endpoints according to eGFR groups are shown in *Table 2*. In regard to the main primary efficacy endpoint (weight loss at 72 h), a greater difference was observed with HCTZ compared to the placebo in patients with better baseline eGFR values, with a difference of −2.1 kg, −1.3 kg, and −0.1 kg in groups 1, 2, and 3, respectively. However, the *p*-value for the eGFR interaction was not significant ($p = 0.246$), meaning that treatment effect in this outcome was not statistically different depending on eGFR group.

For weight loss at 96 h, the differences among the groups were not significant, with a difference in effect between HCTZ and the placebo of −1.8 kg, −1.4 kg, and −0.5 kg in groups 1, 2, and 3, respectively (*p*-value for interaction = 0.256). *Figure 1* shows the graphical representation of weight loss at 72 and 96 h for the two treatment arms and the three eGFR groups.

Regarding patient-reported dyspnoea (endpoint for which no differences were found in the main results of the trial), there was also no interaction between changes in dyspnoea visual analogue scale area under the curve values and the three eGFR groups (*p*-values for interaction 0.241 and 0.271 at 72 and 96 h, respectively).

In terms of 24-h urine volume, the overall results of the trial were significantly favourable to HCTZ, with a difference of 331 ml compared to the placebo. When stratifying the results by eGFR, a similar difference was found in groups 2 and 3 (205 and 377 ml) and a greater difference (716 ml) was found in group 1 (*p*-value for interaction = 0.086).

When analysing weight loss per 40 mg of furosemide, no significant interactions were observed in relation to the eGFR groups at either 72 or 96 h ($p = 0.346$ and $p = 0.464$). *Figure 2* shows these results graphically.

Finally, the effect of eGFR on weight changes at 72 and 96 h when analysing eGFR on a continuous spectrum is shown as restricted cubic spline curves in *Figure 3*. Upon analysing eGFR as a continuous variable, it was observed that the results of the intervention with HCTZ were superior to the placebo across the entire eGFR spectrum and that the effect of HCTZ was most pronounced in patients with high eGFR levels. This continuous quantitative analysis was also carried out for the other efficacy endpoints, but no significant interactions were found between the trial intervention and eGFR classification (online supplementary *Figure S1*).

Effect of estimated glomerular filtration rate on the treatment effect for mortality and rehospitalizations

In the CLOROTIC trial, 18% of patients died and 36% were hospitalized within the 90-day follow-up period, with no significant differences between the two treatment groups (HCTZ vs. placebo). In this post-hoc stratified analysis, the eGFR interaction terms *p*-values were not significant for 30- and 90-day mortality ($p = 0.457$ and $p = 0.693$). On the other hand, patients in group 1 had a significantly lower mortality risk – a difference observed in both the placebo and the HCTZ groups – with an estimated hazard ratio (group 1 vs. group 3) of 0.21 (95% CI 0.06–0.68, $p = 0.009$).

Finally, regarding all-cause rehospitalizations, there were no significant interactions related to eGFR group at 30 or 90 days of follow-up.

The results of the treatment effect on mortality and rehospitalizations stratified according to the eGFR group are shown in *Table 3*. In addition, a continuous quantitative analysis was also carried out for these endpoints; no significant interactions between the trial intervention and eGFR stratification were found (online supplementary *Figure S2*).

Effect of estimated glomerular filtration rate on the treatment effect for safety endpoints

The main results of the CLOROTIC trial showed that patients randomized into the HCTZ arm more frequently experienced worsening renal function, but significant differences in this endpoint were not observed across the three eGFR groups in this post-hoc analysis. Regarding hyponatraemia and hypokalaemia, the results were also similar for the different cut-off values defined in the CLOROTIC trial (125 and 130 mmol/L for sodium and 2.5, 3.0, and 3.5 mmol/L for potassium), with no differences in the proportion of patients with abnormal values of these electrolytes in the overall trial results or when stratifying according to eGFR (*Table 3* and online supplementary *Figure S3*).

Finally, there were no significant differences in hyperkalaemia (defined as potassium levels >5.0 mmol/L), which was similar

Table 1 Baseline characteristics according to estimated glomerular filtration rate on admission

	Group 3 ($n = 121$) <45 ml/min/1.73 m^2	Group 2 ($n = 55$) 45–59 ml/min/1.73 m^2	Group 1 ($n = 54$) ≥60 ml/min/1.73 m^2	*p*-value
Randomized treatment (placebo/HCTZ)	60/61	28/27	28/26	–
Age (years)	83.0 [78.0–88.0]	82.0 [73.5–86.5]	82.0 [78.0–86.0]	0.109
Female sex, *n* (%)	62 (51.2)	23 (41.8)	26 (48.1)	0.511
Systolic blood pressure (mmHg)	127 [112–140]	126 [111–140]	124 [11 8–138]	0.776
Heart rate (bpm)	75.0 [64.0–87.0]	75.0 [69.0–84.5]	77.5 [69.0–88.8]	0.535
Baseline weight (kg)	76.4 [65.0–88.4]	82.4 [75. 2-91.4]	76.0 [63.1–85.8]	0.019
Body mass index (kg/m^2)	29.8 [25.8–33.6]	31.6 [28.2–35.9]	28.1 [25. 7–33.1]	0.038
Medical history, *n* (%)				
Hypertension	107 (88.4)	49 (89.1)	49 (90.7)	0.902
Diabetes	67 (55.4)	35 (63.6)	28 (51.9)	0.432
Atrial fibrillation or flutter	83 (68.6)	35 (63.6)	40 (74.1)	0.501
Anaemia	65 (53.7)	19 (34.5)	19 (35.2)	0.016
Ischaemic cardiomyopathy	42 (34.7)	17 (30.9)	16 (30.2)	0.797
Pacemaker	28 (23.1%)	15 (27.3%)	6 (11.1%)	0.093
Stroke	16 (13.2%)	8 (14.5%)	7 (13.0%)	0.964
COPD	22 (18.2%)	15 (27.3%)	15 (27.8%)	0.239
Clinical features of heart failure				
NYHA functional class, *n* (%)				
I	3 (2.50)	2 (3.64)	1 (1.85)	0.475
II	39 (32.5)	23 (41.8)	20 (37.0)	
III	65 (54.2)	22 (40.0)	30 (55.6)	
IV	13 (10.8)	8 (14.5)	3 (5.56)	
LVEF (%)	55.0 [40.0–62.8]	54.5 [39. 2–60.0]	60.0 [37. 5–63.5]	0.405
HFpEF (LVEF ≥50%), *n* (%)	73 (64.0)	34 (63.0)	36 (70.6)	0.552
Hospitalization for HF within previous 12 months, *n* (%)	75 (62.0)	33 (60.0)	30 (55.6)	0.725
Emergency room visits for HF within previous 12 months, *n* (%)	79 (65.3)	36 (65.5)	29 (53.7)	0.303
Analytical parameters				
Sodium (mmol/L)	139 [137–142]	140 [137–142]	139 [136–142]	0.847
Potassium (mmol/L)	4.40 [4.00–4.80]	4.11 [3.88–4.60]	4.00 [3.70–4.55]	0.001
Magnesium (mmol/L)	2.07 [1.78–2.30]	1.96 [1.52–2.12]	2.05 [1.78–2.17]	0.056
BNP (pg/ml)	1458 [627–3264]	604 [378–1208]	534 [472–2390]	0.254
NT-proBNP (pg/ml)	5995 [2902–10 179]	5393 [2077–9000]	3431 [1868–4936]	0.004
Medications				
ACE inhibitor or ARB, *n* (%)	56 (46.3)	36 (65.5)	35 (64.8)	0.016
Beta-blocker, *n* (%)	70 (57.9)	34 (61.8)	35 (64.8)	0.665
MRA (25 mg/day), *n* (%)	33 (27.3)	25 (45.5)	23 (42.6)	0.028
Oral furosemide dose (mg/day)	80.0 [80.0–120]	80.0 [80.0–120]	80.0 [80.0–100]	0.573

Values are median [interquartile range] unless otherwise indicated.
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HCTZ, hydrochlorothiazide; HF, heart failure; HFpEF, 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.

between the two groups in the overall trial (22.4% and 21.9% in those assigned to placebo and HCTZ, respectively) and among the three eGFR groups ($p = 0.693$).

Discussion

This post-hoc analysis of the CLOROTIC trial analyses the efficacy and safety of a combination diuretic strategy (HCTZ in addition to loop diuretics) in AHF across the entire baseline eGFR spectrum. The effect of combination diuretic treatment on the primary efficacy endpoint of the trial (weight loss at 72 h) weakens as eGFR worsens. The results are similar when analysing metrics of diuretic response according to eGFR. Adding HCTZ to loop diuretic therapy therefore seems to improve diuretic response – albeit at a slightly different pace in the presence of low baseline eGFR values – in all patients with AHF regardless of baseline eGFR.

In terms of safety, the addition of HCTZ did not entail an increased risk of mortality, rehospitalizations, worsening renal

Table 2 Treatment effect for primary and secondary efficacy endpoints for the three categorical estimated glomerular filtration rate groups

Endpoint	Results for placebo	Results for HCTZ	Median difference (95% CI)	*p*-value*
Primary endpoints				
Change in weight (kg) at 72 h				
Overall	−1.6 (−2.1 to −1.1)	−2.4 (−2.7 to −1.8)	−0.8 (−1.4 to −0.2)	0.001
<45 ml/min/1.73 m^2	−1.8 (−2.3 to −0.9)	−1.9 (−2.4 to −1.7)	−0.1 (−1.3 to 0.4)	0.246**
45–59 ml/min/1.73 m^2	−1.2 (−2.1 to −0.7)	−2.5 (−3.3 to −0.9)	−1.3 (−2.3 to 0.2)	
≥60 ml/min/1.73 m^2	−1.6 (−2.9 to −1.2)	−3.7 (−4.8 to −2.7)	−2.1 (−3.0 to −0.5)	
AUC for dyspnoea at 72 h (VAS scale)				
Overall	720 (603 to 955)	960 (491 to 1171)	240 (−250 to 438)	0.708
<45 ml/min/1.73 m^2	802 (567 to 1176)	747 (543 to 940)	−55 (−394 to 352)	0.241
45–59 ml/min/1.73 m^2	978 (557 to 1420)	1057 (761 to 1574)	79 (−394 to 716)	
≥60 ml/min/1.73 m^2	660 (441 to 862)	1300 (750 to 1796)	640 (130 to 1321)	
Secondary endpoints				
Change in weight (kg) at 96 h				
Overall	−1.5 (−1.9 to −1.1)	−2.6 (−3.3 to −2.1)	−1.2 (−2.0 to −0.3)	<0.001
<45 ml/min/1.73 m^2	−1.6 (−1.9 to −0.9)	−2.1 (−2.5 to −1.8)	−0.5 (−1.3 to −0.1)	0.256
45–59 ml/min/1.73 m^2	−1.4 (−2.1 to −0.6)	−2.7 (−3.8 to −1.4)	−1.4 (−2.6 to 0.3)	
≥60 ml/min/1.73 m^2	−2.0 (−4.5 to −1.1)	−3.8 (−4.7 to −3.3)	−1.8 (−3.0 to −0.3)	
AUC for dyspnoea at 96 h (VAS scale)				
Overall	1320 (1007 to 1593)	1560 (1192 to 1774)	240 (−209 to 573)	0.768
<45 ml/min/1.73 m^2	1268 (958 to 1695)	1303 (875 to 1715)	34 (−771 to 580)	0.271
45–59 ml/min/1.73 m^2	1824 (951 to 2433)	1702 (1305 to 2043)	−122 (−1054 to 694)	
≥60 ml/min/1.73 m^2	1126 (814 to 1330)	1689 (1249 to 3017)	563 (103 to 1893)	
24-h diuresis quantification (ml)				
Overall	1430 (1365 to 1536)	1761 (1534 to 1920)	331 (100 to 509)	0.019
<45 ml/min/1.73 m^2	1440 (1324 to 1536)	1645 (1486 to 1741)	205 (−31 to 313)	0.086**
45–59 ml/min/1.73 m^2	1381 (1186 to 1863)	1757 (1426 to 1921)	377 (−168 to 652)	
≥60 ml/min/1.73 m^2	1569 (1169 to 2034)	2285 (1964 to 3086)	716 (172 to 1297)	
Weight loss per 40 mg furosemide (from baseline to 72 h)				
Overall	−0.2 (−0.3 to −0.1)	−0.4 (−0.5 to −0.3)	−0.2 (−0.3 to −0.03)	0.001
<45 ml/min/1.73 m^2	−0.2 (−0.3 to −0.1)	−0.3 (−0.4 to −0.2)	−0.1 (−0.3 to −0.03)	0.346
45–59 ml/min/1.73 m^2	−0.3 (−0.4 to −0.05)	−0.4 (−0.6 to −0.2)	−0.1 (−0.5 to 0.1)	
≥60 ml/min/1.73 m^2	−0.2 (−0.4 to −0.2)	−0.6 (−0.7 to −0.4)	−0.4 (−0.5 to −0.1)	
Weight loss per 40 mg furosemide (from baseline to 96 h)				
Overall	−0.2 (−0.2 to −0.1)	−0.4 (−0.5 to −0.3)	−0.2 (−0.3 to −0.1)	<0.001
<45 ml/min/1.73 m^2	−0.1 (−0.2 to −0.08)	−0.3 (−0.4 to −0.3)	−0.2 (−0.3 to −0.1)	0.464
45–59 ml/min/1.73 m^2	−0.2 (−0.3 to −0.04)	−0.4 (−0.5 to −0.2)	−0.2 (−0.4 to 0.06)	
≥60 ml/min/1.73 m^2	−0.2 (−0.3 to −0.1)	−0.5 (−0.6 to −0.4)	−0.3 (−0.4 to −0.1)	
Net fluid loss (ml) per 40 mg of furosemide (from baseline to 72 h)				
Overall	726 (672 to 812)	810 (740 to 878)	83 (−4.56 to 184)	0.152
<45 ml/min/1.73 m^2	695 (550 to 750)	731 (674 to 799)	36 (−48 to 147)	0.803**
45–59 ml/min/1.73 m^2	785 (669 to 932)	828 (807 to 970)	43 (−76 to 255)	
≥60 ml/min/1.73 m^2	816 (562 to 987)	886 (774 to 1222)	69 (−1 423 526)	

AUC, area under the curve; CI, confidence interval; eGFR, estimated glomerular filtration rate; HCTZ, hydrochlorothiazide; VAS, visual analogue scale.

*For each outcome, the first *p*-value assesses the adjusted median difference between HCTZ and placebo on the analysed outcome by comparing the model with it and adjusted by the weight and the set of unbalanced variables at baseline with the model without treatment. Equivalently, the second *p*-value assesses the adjusted interaction effect between the treatment and eGFR groups on the analysed outcome by comparing the model with it and their main effects and adjusted by the same variables with the model without this interaction. The ANOVA function with rank test and normal score for quantile regression models was used. Safety endpoints captured any event observed at any time throughout the study. The estimated median in each group and their difference are provided together with their 95% CI except for both primary outcomes for which the 97.5% CI is reported.

**Outcomes for which no significant interaction but a significant main effect of eGFR was observed.

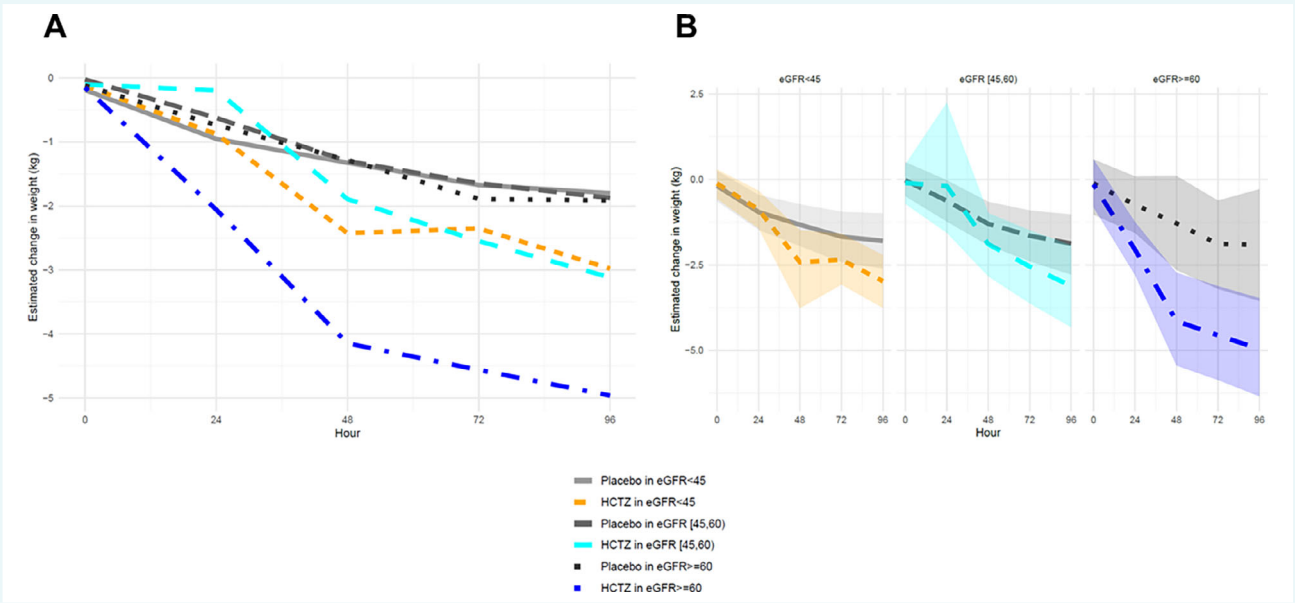


Figure 1 Changes in weight at 72 and 96 h after randomization in the two treatment arms (hydrochlorothiazide [HCTZ] or placebo) and the three estimated glomerular filtration rate (eGFR) groups (*A*). Changes in weight stratified by eGFR groups with 95% confidence interval (*B*).

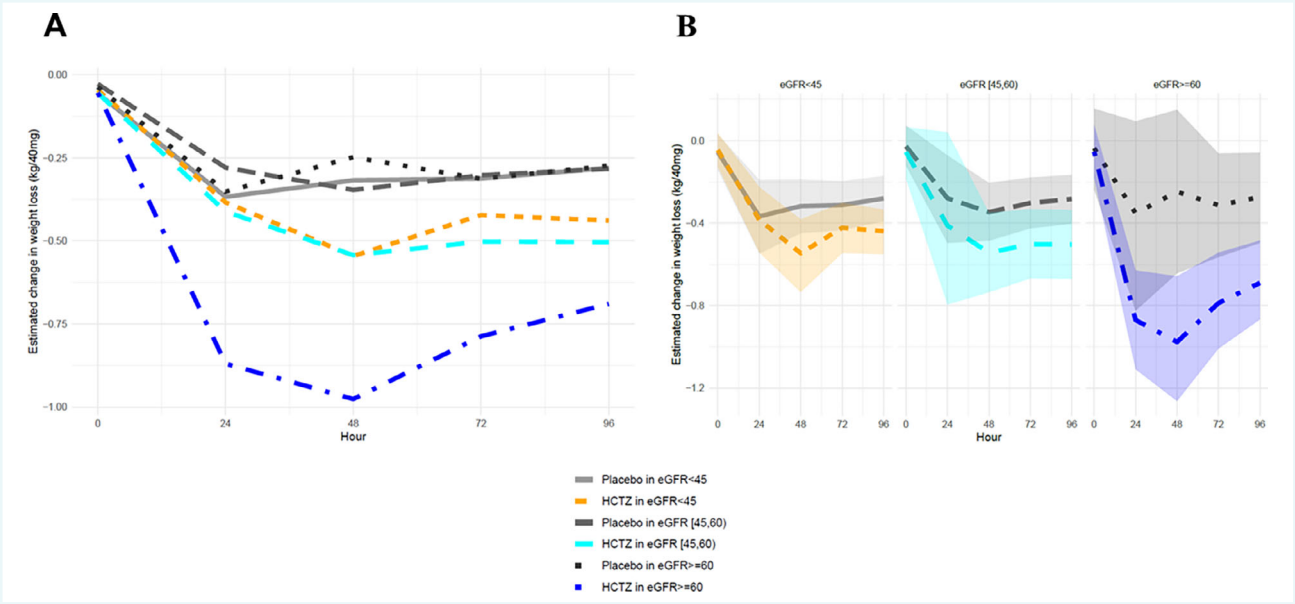


Figure 2 Metric of diuretic response (changes in weight per 40 mg of furosemide) at 72 and 96 h after randomization for the two treatment arms (hydrochlorothiazide [HCTZ] or placebo) and the three estimated glomerular filtration rate (eGFR) groups (*A*). Changes in weight per 40 mg of furosemide stratified by eGFR groups with 95% confidence interval (*B*).

function, or electrolyte disturbances in patients with more advanced degrees of renal failure.

One of the strengths of the CLOROTIC trial was the inclusion of all patients regardless of eGFR value upon admission (except if the patient required renal replacement therapy). More than half of patients had eGFR values below 45 ml/min/1.73 m^2; this subgroup of patients is frequently underrepresented in clinical trials, especially those with an eGFR lower than 20 ml/min/1.73 m^2 or serum creatinine values greater than 3.0 mg/dl (265.2 μmol/L).[8,9] Their inclusion is especially relevant in light of the longstanding uncertainty concerning the diuretic effect of HCTZ in patients with low eGFR values.[2,5] Indeed, recent studies have shown

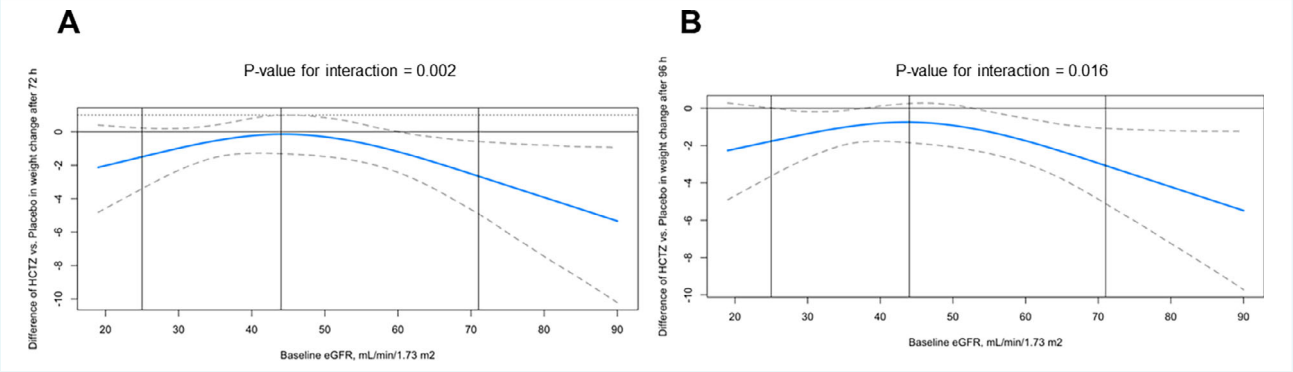


Figure 3 Restricted cubic spline curves showing the differences in weight at 72 h (*A*) and 96 h (*B*) according to estimated glomerular filtration rate (eGFR) as a continuous variable. HCTZ, hydrochlorothiazide.

that combination regimens are more effective than the use of HCTZ or furosemide alone for increasing natriuresis or controlling blood pressure in patients with advanced chronic kidney disease.[6,10]

The diminished response to diuretics in the presence of chronic kidney disease is a consequence of impaired drug delivery to the site of action. Given that diuretics must reach the lumen of the nephron to be effective, higher doses are required in patients with renal insufficiency than in other patients.[11] In the CLOROTIC study, the strategy was to modify the dose of HCTZ according to eGFR category, using higher doses with lower eGFR values. The results of this study seem to confirm that this strategy is useful for maintaining an effective diuretic response (which is more delayed in patients with lower eGFR values) with no additional increase in adverse events.

Worsening renal function (WRF) occurs in 20–30% of patients with AHF and has been classically associated with greater morbidity and mortality, although there is controversy regarding the precise pathogenic mechanism.[12] A physiological renal response to the increased diuresis associated with WRF might not necessarily be related to worse clinical outcomes. More recent research that interprets WRF in the context of decongestion in AHF suggests that its association with clinical outcomes depends on diuretic response. In two large cohorts of patients with AHF, WRF in the first 4 days was not associated with worse outcomes when patients had a good diuretic response.[13,14] In the CLOROTIC trial, WRF occurred more frequently in patients who received HCTZ (with no differences when stratified according to eGFR), but it was not associated with an increase in mortality or rehospitalizations during the follow-up period. This finding should reaffirm the notion that short-term diuretic-induced reductions in eGFR do not portend worse outcomes, at least with respect to renal failure, rehospitalizations due to HF, and survival. It has been reported that a moderate increase in creatinine might indeed be a useful marker of effective diuresis in AHF.[15] Nevertheless, renal function often changes dynamically before, during, and immediately following AHF admissions and a substantial proportion of such admissions result in WRF. Kidney function decline may occur in advance of episodes of decompensation and can continue following recovery from hospitalization.[16]

Recent trials have renewed interest in thiazides for controlling volume overload and hypertension in all chronic kidney disease stages, including severe and end-stage disease (IV and V). But not all thiazide or thiazide-like diuretics have the same pharmacological properties and efficacy.[17] All yield a similar effect by blocking the sodium–chloride co-transporter in the distal convoluted tubule, but they differ in terms of half-lives and off-target effects.[7,18] For this reason, in the authors' opinion, the efficacy and safety results of the CLOROTIC trial with HCTZ cannot be extrapolated to other thiazide diuretics with longer half-lives (e.g. metolazone and chlorthalidone) and perhaps more powerful and sustained effects.

Several limitations of this study should be acknowledged. First, this is a post-hoc analysis of the CLOROTIC trial, which was only powered to test the treatment effect in the total study cohort. Second, there was no multiple testing correction, making this rather small study prone to spurious findings. Third, a large relative yet small absolute overall amount of weight loss was observed and, as there was no specific requirement for a given 'amount' of congestion at inclusion, it stands to reason that if more volume overloaded patients had been enrolled, larger absolute reductions in weight may have been observed. Fourth, all patients had a history of chronic HF and required moderate-to-high doses of loop diuretics before admission. Therefore, these findings cannot be generalized to patients with newly diagnosed HF who are diuretic naïve or have lower prior loop diuretic use. Fifth, not all patients enrolled in the trial had a urinary catheter to quantify fluid loss and the accuracy of urine volume quantification in the absence of catheterization may be variable and inaccurate for precisely defining the diuretic response. Finally, eGFR was not monitored in the follow-up visits, so it cannot be guaranteed that WRF was transient (resolved after discharge) and merely a marker of good diuretic response.

In conclusion, adding eGFR-adjusted doses of oral HCTZ to intravenous furosemide improved the diuretic response in patients with acutely decompensated chronic HF. This effect was independent of baseline eGFR although tended to be larger at higher eGFR.

Table 3 Treatment effect for mortality, rehospitalizations and safety endpoints for the three categorical estimated glomerular filtration rate groups

Endpoint	Results for placebo	Results for HCTZ	Model estimated effect	*p*-value*
Secondary endpoints			**Hazard ratio (95% CI)**	
All-cause mortality at 30 days				
Overall	7/116	11/114	1.53 (0.58–4.04)	0.389
<45 ml/min/1.73 m^2	5/60	7/61	1.58 (0.49–5.09)	0.457
45–59 ml/min/1.73 m^2	2/28	3/27	0.81 (0.11–6.04)	
≥60 ml/min/1.73 m^2	0/28	1/26	Non-estimable value	
All-cause mortality at 90 days				
Overall	19/116	23/114	1.23 (0.66–2.28)	0.510
<45 ml/min/1.73 m^2	14/60	16/61	1.27 (0.61–2.62)	0.693**
45–59 ml/min/1.73 m^2	4/28	5/27	0.80 (0.19–3.29)	
≥60 ml/min/1.73 m^2	1/28	2/26	2.55 (0.23–28.14)	
All-cause rehospitalizations at 30 days				
Overall	18/116	27/114	1.64 (0.90–2.98)	0.101
<45 ml/min/1.73 m^2	9/60	17/61	1.88 (0.84–4.22)	0.848
45–59 ml/min/1.73 m^2	5/28	6/27	1.34 (0.41–4.41)	
≥60 ml/min/1.73 m^2	4/28	4/26	1.29 (0.32–5.18)	
All-cause rehospitalizations at 90 days				
Overall	39/116	43/114	1.24 (0.80–1.91)	0.338
<45 ml/min/1.73 m^2	22/60	27/61	1.29 (0.73–2.26)	0.722
45–59 ml/min/1.73 m^2	10/28	8/27	0.88 (0.34–2.24)	
≥60 ml/min/1.73 m^2	7/28	8/26	1.49 (0.54–4.10)	
Safety endpoints			**Odds ratio (95% CI)**	
Impaired renal function (increase in creatinine levels >26.5 μmol/L)				
Overall	20/116	53/114	4.15 (2.29–7.75)	<0.001
<45 ml/min/1.73 m^2	11/60	32/61	4.91 (2.20–11.59)	0.356
45–59 ml/min/1.73 m^2	3/28	12/27	6.62 (1.77–32.7)	
≥60 ml/min/1.73 m^2	6/28	9/26	1.94 (0.58–6.80)	
Hyponatraemia (sodium level ≤130 mmol/L)				
Overall	6/116	10/114	1.73 (0.62–5.25)	0.299
<45 ml/min/1.73 m^2	5/60	5/61	0.97 (0.26–3.68)	0.220
45–59 ml/min/1.73 m^2	0/28	2/27	Non-estimable value	
≥60 ml/min/1.73 m^2	1/28	3/26	3.50 (0.41–73.46)	
Hyponatraemia (sodium level ≤125 mmol/L)				
Overall	2/116	3/114	1.69 (0.27–13.29)	0.570
<45 ml/min/1.73 m^2	2/60	1/61	0.51 (0.02–5.55)	0.198
45–59 ml/min/1.73 m^2	0/28	1/27	Non-estimable value	
≥60 ml/min/1.73 m^2	0/28	1/26	Non-estimable value	
Hypokalaemia (potassium levels ≤3.5 mmol/L)				
Overall	22/116	51/114	3.43 (1.92–6.31)	<0.001
<45 ml/min/1.73 m^2	9/60	23/61	3.42 (1.46–8.58)	0.965
45–59 ml/min/1.73 m^2	6/28	13/27	3.34 (1.06–11.50)	
≥60 ml/min/1.73 m^2	7/28	15/26	4.07 (1.32–13.62)	
Hypokalaemia (potassium levels ≤3.0 mmol/L)				
Overall	3/116	13/114	4.76 (1.48–21.21)	0.007
<45 ml/min/1.73 m^2	2/60	6/61	3.13 (0.68–22.01)	0.374
45–59 ml/min/1.73 m^2	0/28	4/27	Non-estimable value	
≥60 ml/min/1.73 m^2	1/28	3/26	3.53 (0.42–74.54)	
Hypokalaemia (potassium levels ≤2.5 mmol/L)				
Overall	0/116	2/114	Non-estimable value	0.086
<45 ml/min/1.73 m^2	0/60	0/61	Non-estimable value	Non-estimable value
45–59 ml/min/1.73 m^2	0/28	1/27	Non-estimable value	
≥60 ml/min/1.73 m^2	0/28	1/26	Non-estimable value	

CI, confidence interval; eGFR, estimated glomerular filtration rate; HCTZ, hydrochlorothiazide.

*For each outcome, the first *p*-value assesses the adjusted relative measure (HR or OR) of HCTZ vs. placebo on the analysed outcome by comparing the model with it and adjusted by the weight and the set of unbalanced variables at baseline with the model without treatment. Equivalently, the second *p*-value assesses the adjusted interaction effect between the treatment and eGFR groups on the analysed outcome by comparing the model with it and their main effects and adjusted by the same variables with the model without this interaction. The analysis of deviance to compare two Cox regression models and the likelihood ratio test to compare logistic regression models were used. Safety endpoints captured any event observed at any time throughout the study.

**Outcomes for which no significant interaction but a significant main effect of eGFR was observed.

HCTZ therapy was associated with higher rates of worsening renal function and hypokalaemia (*Graphical Abstract*).

Supplementary Information

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

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Appendix

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