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Combining Loop and Thiazide Diuretics Across the Left Ventricular Ejection Fraction Spectrum

The CLOROTIC Trial

Marta Sánchez-Marteles, MD, PhD,[a,b] Vanesa Garcés-Horna, MD, PhD,[a,b] José Luís Morales-Rull, MD, PhD,[c] Jesús Casado, MD, PhD,[d] Margarita Carrera-Izquierdo, PhD,[e] Alicia Conde-Martel, MD, PhD,[f] Melitón Francisco Dávila-Ramos, MD, PhD,[g] Pau Llácer, PhD,[h] Prado Salamanca-Bautista, MD, PhD,[i] Raúl Ruiz, PhD,[j] Oscar Aramburu-Bodas, MD, PhD,[i] Francesc Formiga, MD, PhD,[k] Luís Manzano, MD, PhD,[j] Joan Carles Trullàs, MD, PhD[l,m]

ABSTRACT

BACKGROUND The addition of hydrochlorothiazide (HCTZ) to furosemide in the CLOROTIC (Combining Loop with Thiazide Diuretics for Decompensated Heart Failure) trial improved the diuretic response in patients with acute heart failure (AHF).

OBJECTIVES This work aimed to evaluate if these results differ across the spectrum of left ventricular ejection fraction (LVEF).

METHODS This post hoc analysis of the randomized, double-blind, placebo-controlled CLOROTIC trial enrolled 230 patients with AHF to receive either HCTZ or a placebo in addition to an intravenous furosemide regimen. The influence of LVEF on primary and secondary outcomes was evaluated.

RESULTS The median LVEF was 55%: 166 (72%) patients had LVEF >40%, and 64 (28%) had LVEF ≤40%. Patients with a lower LVEF were younger, more likely to be male, had a higher prevalence of ischemic heart disease, and had higher natriuretic peptide levels. The addition of HCTZ to furosemide was associated with the greatest weight loss at 72 of 96 hours, better metrics of diuretic response, and greater 24-hour diuresis compared with placebo, with no significant differences according to the LVEF category (using 2 LVEF cutoff points: 40% and 50%) or LVEF as a continuous variable (all *P* values were insignificant). There were no significant differences observed with the addition of HCTZ in terms of mortality, rehospitalizations, or safety endpoints (impaired renal function, hyponatremia, and hypokalemia) among the 2 LVEF groups (all *P* values were insignificant).

CONCLUSIONS Adding HCTZ to intravenous furosemide seems to be effective strategy for improving diuretic response in AHF without treatment effect modification according to baseline LVEF. (Combining Loop with Thiazide Diuretics for Decompensated Heart Failure [CLOROTIC], NCT01647932; Randomized, double blinded, multicenter study, to asses Safety and Efficacy of the Combination of Loop With Thiazide-type Diuretics vs Loop diuretics with placebo in Patients With Decompensated, EudraCT Number 2013-001852-36) (J Am Coll Cardiol HF 2024;■:■–■) © 2024 by the American College of Cardiology Foundation.

From the [a]Internal Medicine Department, Hospital Clínico Universitario "Lozano Blesa," Calle de San Juan Bosco, Zaragoza, Spain; [b]Aragon Health Research Institute (IIS Aragon), Zaragoza, Spain; [c]Internal Medicine Department, Heart Failure Unit, Hospital Universitari Arnau de Villanova, Institut de Recerca Biomédica (IRBLleida), Avinguda Alcalde Rovira Roure, Lleida, Spain; [d]Internal Medicine Department, Hospital Universitario de Getafe, Carretera de Madrid-Toledo, Madrid, Spain; [e]Internal Medicine Department, Complejo Hospitalario de Soria, Paseo Santa Bárbara, Soria, Spain; [f]Internal Medicine Department, Hospital Universitario de Gran Canaria Dr. Negrín, C. Pl. Barranco de la Ballena, Las Palmas de Gran Canaria, Spain; [g]Internal Medicine Department, Hospital Universitario Nuestra Señora de la Candelaria, Carretera General del Rosario, Santa Cruz de Tenerife, Spain; [h]Internal Medicine Department, Hospital de Manises, Avinguda de la Generalitat Valenciana, Manises, Valencia, Spain; [i]Internal Medicine Department, Hospital Universitario Virgen Macarena, Universidad de Sevilla, Avenida Dr. Fedriani, Sevilla, Spain;

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ABBREVIATIONS AND ACRONYMS

AHF = acute heart failure

eGFR = estimated glomerular filtration rate

GDMT = guideline-directed medical therapy

HCTZ = hydrochlorothiazide

HF = heart failure

HFmrEF = heart failure with mildly reduced ejection fraction

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

LVEF = left ventricular ejection fraction

Acute heart failure (AHF) is an important health care problem in developed countries. It is the leading cause of hospitalization in older adults,[1,2] and signs and symptoms of congestion are the main cause of hospital admission.[3] Intravenous loop diuretics are often the first drug provided and are the cornerstone of AHF congestion treatment. However, a large number of patients have an insufficient diuretic response, which has been linked to worse outcomes, including an increase in mortality and readmissions.[4,5]

The phenotyping of heart failure (HF) throughout the left ventricular ejection fraction (LVEF) is still an open debate,[6] and cases of HF with preserved and reduced ejection fraction have relevant differences in their clinical and physiopathological characteristics and also in their response to guideline-directed medical therapies (GDMTs).[7,8] HF with preserved ejection fraction (HFpEF) is a more heterogeneous syndrome with microvascular and endothelial dysfunction and different biological phenotypes. In contrast, neurohormonal and sympathetic system activation plays a predominant role in HF with reduced ejection fraction (HFrEF).[8] Thus, although there are differences in GDMT recommendations depending on the LVEF category, the treatment of congestion in AHF does not differ according to LVEF.

Different treatment strategies that combine diuretics have recently been evaluated.[9,10] The CLOROTIC (Combining Loop with Thiazide Diuretics for Decompensated Heart Failure) trial evaluated the effect of adding hydrochlorothiazide (HCTZ) to intravenous furosemide on diuretic response in patients admitted for AHF regardless of baseline treatment with loop diuretics.[10,11] This trial determined that adding HCTZ to loop diuretics improved diuretic response in patients with AHF, an important finding.[10] The effect of HCTZ on the primary endpoint was generally consistent across different subgroups, including the LVEF.

However, the effect of this combined treatment strategy on patients in different LVEF and HF categories (reduced, mildly reduced, and preserved) remains unknown. For all these reasons, it seemed appropriate to analyze this aspect in greater depth. With the aforementioned pathophysiological differences and response to GDMT, we hypothesized that there could be differences in the response to diuretic treatment in patients with AHF and congestion depending on the LVEF.

The present study was an exploratory and post hoc analysis of the CLOROTIC trial that aimed to assess the diuretic response to HCTZ in patients across the LVEF spectrum. To do so, the influence of baseline LVEF on the primary and secondary endpoints (changes in body weight at 72 and 96 hours after randomization, metrics of diuretic response, and mortality/rehospitalizations during the follow-up period) and safety endpoints was analyzed.

METHODS

TRIAL DESIGN AND PARTICIPANTS. The CLOROTIC study was a multicenter, 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. The details of the design (including the loop diuretic treatment protocol during the randomization phase) and the main results of the trial have previously been published.[10,11] Briefly, patients aged ≥18 years with a history of chronic HF and a hospital admission due to AHF who received oral maintenance therapy with at least 80 mg of furosemide (or an equivalent dose in the case of a different loop diuretic) for at least 1 month were eligible to participate. Evaluation of LVEF with an echocardiogram (performed in the echocardiography laboratories at the local sites) was mandatory in the study. Echocardiography should preferably be performed during hospitalization and, if it could not be performed during admission, data could be obtained from an echocardiogram performed within the 3 months before admission.

[j]Internal Medicine Department, Hospital Universitario Ramón y Cajal, IRYCIS, Universidad de Alcalá, Madrid, Spain; [k]Internal Medicine Department, Hospital Universitari de Bellvitge, IDIBELL, Carrer de la Feixa Llarga, L'Hospitalet de Llobregat, Barcelona, Spain; [l]Internal Medicine Department, Hospital d'Olot i Comarcal de la Garrotxa, Avinguda dels Països Catalans Olot, Girona, Spain; and the [m]Tissue Repair and Regeneration Laboratory (TR2Lab), Institut de Recerca i Innovació en Ciències de la Vida i de la Salut a la Catalunya Central (IrisCC), Ctra. de Roda, Barcelona, Spain.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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Patients were excluded if they were unstable on admission (acute coronary syndrome, cardiogenic shock, and/or intensive care unit admission), treated with inotropic agents, or received any thiazide-type 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 (any estimated glomerular filtration rate [eGFR] on admission was acceptable) except if the patient required renal replacement therapy. Hypokalemia and hyponatremia were exclusion criteria if potassium or sodium values at randomization were ≤2.5 or 125 mmol/L (or any symptomatic sodium value), respectively.

ETHICAL APPROVAL. The study complied with the Declaration of Helsinki and was approved by the Spanish Agency of Medicines and Medical Devices (AEMPS [for its initials in Spanish]) and the local institutional ethics committees at each center. All patients provided written informed consent.

TRIAL INTERVENTION. Within the first 24 hours after hospital admission, patients were randomly assigned at a 1:1 ratio to receive HCTZ or a placebo for 5 days, both of which were supplied as oral tablets. Oral HCTZ doses were adjusted according to eGFR using the MDRD (Modification of Diet in Renal Disease) formula as follows: >50 mL/min: 25 mg daily; 20 to 50 mL/min: 50 mg daily; and <20 mL/min: 100 mg daily. Patients received the same HCTZ dose during the treatment period; up-titration or down-titration was not permitted. The dose of HCTZ (or placebo) could only be adjusted based on changes in eGFR observed during the treatment period. To ensure homogeneous intravenous loop diuretic administration in all participating centers, an algorithm for furosemide dosage was recommended, based on the low-dose arm of the DOSE-AHF (Diuretic Optimal Strategy Evaluation in Acute Heart Failure) trial.[12] All patients were monitored during the study medication period, until hospital discharge, and then for an additional safety period of 90 days after discharge.[10,11]

ENDPOINTS. The primary efficacy endpoints were changes in body weight and changes in patient-reported dyspnea from baseline to 72 hours after randomization. Prespecified secondary endpoints included the following: changes in body weight and patient-reported dyspnea 96 hours 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-hour diuresis quantification, weight loss per 40 mg of furosemide (at 72 and 96 hours), net fluid loss (24-hour diuresis) per milligram of furosemide, and mean loop diuretic dose administered from the time of study enrollment up to 72 hours. 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 0.3 mg/dL) and/or a decrease in serum eGFR >50% compared with baseline levels. Hypokalemia and hyponatremia were defined as potassium levels ≤2.5 mmol/L and sodium levels ≤125 mmol/L, respectively. A post hoc analysis using higher sodium (<130 mmol/L) and potassium (<3.5 and <3.0 mmol/L) cutoff values was also conducted.

LEFT VENTRICULAR EJECTION FRACTION. This post hoc study evaluated whether LVEF at the time of randomization had an influence on the trial's primary, secondary, and safety outcomes. It was conducted by using 2 groups of the LVEF categories: LVEF ≤40% vs LVEF >40%. The rationale for not performing this comparison using the 3 HF categories defined according to the European Society of Cardiology HF guidelines (HF with reduced, mildly reduced, or preserved LVEF) was due to the limited number of patients (n = 17) with mildly reduced LVEF (defined as LVEF 41%-49%). An additional analysis using LVEF as a continuous variable was also performed. A sensitivity analysis was also conducted by changing the LVEF cutoff point to 50%.

STATISTICAL ANALYSIS. Summary measures, including quartiles (median, 25th and 75th percentiles) and frequencies (absolute and relative), were calculated for the quantitative and qualitative variables, respectively. Quantitative variables and their changes from baseline were compared in the different LVEF categories by using the Mann-Whitney U test. Qualitative variables were compared among groups by using the Pearson chi-square test or, if expected frequencies were <5, the Fisher exact test.

The statistical significance of the interaction between the randomly assigned treatment and continuous LVEF values was assessed for all primary, secondary, and safety outcomes using regression models. They included restricted cubic splines applied to LVEF (without assuming a linear trend) with 3 knots located at the 10th, 50th, and 90th percentiles in case of a significant nonlinear association with LVEF. The safety endpoints were defined as any event observed at any time throughout the study. The regression models included a quantile regression model for the median for the quantitative outcomes (body weight change, patient-reported dyspnea change, and metrics of diuretic response), Cox

proportional hazards models for the survival outcomes (mortality and rehospitalizations at 30 and 90 days), and a logistic regression model for the binary outcomes (safety outcomes). These regression models were adjusted by weight and age at baseline and the set of unbalanced variables at baseline (all of which were mean centered if quantitative). The statistical significance of the nonlinear association with LVEF was assessed by comparing the model that included cubic splines vs the model without them (linear in LVEF). The statistical significance of the interaction between the treatment and LVEF was assessed by comparing the model that included both main effects and their interaction vs the model that omitted their interaction. The statistical significance of the LVEF classification's main effect (obtained by comparing the model with and the model without it) was provided in the absence of a significant interaction. For all of these comparisons, the analysis of variance function with rank test and normal score was used for quantile regression models (on quantitative outcomes), and the analysis of deviance chi-square test was used for both Cox proportional hazards (on survival outcomes) and logistic regression models (on binary outcomes).

The possible interaction of the treatment (HCTZ or placebo) with the classification of LVEF into levels was also assessed for all primary, secondary, and safety outcomes using regression models. As done previously, the regression models included quantile regression models for the median of the quantitative outcomes, Cox proportional hazards models for the survival outcomes, and a logistic regression model for the binary outcomes. Again, we assessed the statistical significance of the interaction by using the analysis of variance function with rank test and normal score for the comparison of quantile regression models and the analysis of deviance chi-square test for both the comparison of Cox proportional hazards and the comparison of logistic regression models. The statistical significance of the LVEF classification's main effect (obtained by comparing the model with and the model without it) was provided in the absence of a significant interaction.

Mean changes over time (from randomization and throughout the intervention period) in weight loss and in weight loss per 40 mg of furosemide are represented graphically. They were estimated by using linear mixed-effects models with the random effect of the patient and the fixed effects of the baseline variables of weight, age, and the set of unbalanced variables at baseline (all mean centered if quantitative), together with the interaction between the randomized treatment, LVEF classification, and time. No form of trend was assumed for time, but it was introduced as a qualitative variable into the models. A nonparametric cases bootstrap 97.5% CI based on 5,000 replicates (resampling patients) was added to the mean estimates.

The normality and homoskedasticity of the residuals coming from quantile and linear regression models were checked graphically. The Shapiro-Wilk test was used to assess the normal distribution of residuals. For the Cox regression models, we checked the proportional hazards assumption by plotting and testing their scaled Schoenfeld residuals. The calibration of the logistic regression models was also assessed graphically and with the Hosmer-Lemeshow test.

All statistical analyses were performed in R (R Foundation for Statistical Computing) using a significance level of 0.025 (and therefore 97.5% confidence, notionally 95%) for the 2 coprimary outcomes and 0.05 for secondary and safety outcomes. The statistical analysis for secondary and safety outcomes was not adjusted for multiple testing.

RESULTS

PATIENT POPULATION AND BASELINE CHARACTERISTICS ACCORDING TO LVEF. A total of 230 patients were enrolled in the CLOROTIC trial. The median age was 83 years, and 48% were female. The median LVEF was 55% and ranged from 15% to 86%. Sixty-four (28%) patients had HFrEF (LVEF ≤40%), 17 (7%) had heart failure with mildly reduced ejection fraction (HFmrEF) (LVEF 41%-49%), and 149 (65%) had HFpEF (LVEF ≥50%).

For this study, comparisons were made between LVEF groups using the cutoff value of 40%: 166 (72%) patients had LVEF >40%, and 64 (28%) had LVEF ≤40%. In the sensitivity analysis using the 50% LVEF cutoff value, 149 (65%) patients had LVEF ≥50%, and 81 (35%) had LVEF <50%. The baseline characteristics of the patients and comparisons according to the 2 LVEF categories are presented in **Table 1** (Supplemental Table 1 provides details on the 50% cutoff point). Patients with a lower LVEF were younger, more likely to be male, had a higher prevalence of ischemic heart disease, had lower systolic blood pressure and body mass index, and had higher natriuretic peptide values. In addition, more patients in this group received treatment with mineralocorticoid receptor antagonists. The doses of loop diuretic received during hospitalization were similar between the 2 LVEF groups up to 24 hours after randomization. Beyond this time point, the doses were somewhat higher in patients with lower LVEF.

EFFECT OF LVEF ON THE TREATMENT EFFECT FOR PRIMARY AND SECONDARY EFFICACY ENDPOINTS. The results on primary and secondary endpoints according to LVEF are shown in Table 2. Regarding the main primary endpoint (weight loss at 72 hours), a greater difference was observed with HCTZ compared with the placebo in patients with higher baseline LVEF values compared with lower LVEF values (difference of −1.09 and −0.32 kg, respectively). However, the *P* value for the LVEF interaction was not significant ($P = 0.169$), meaning that the treatment effect in this outcome was not statistically different depending on the LVEF group.

For weight loss at 96 hours, the differences between the 2 groups were not significant, with a difference in effect between HCTZ and the placebo of −1.2 kg and −0.57 kg in patients with higher and lower values of LVEF, respectively ($P = 0.663$). Figure 1 shows the graphical representation of weight loss at 72 and 96 hours for the 2 treatment arms and the 2 LVEF groups.

Regarding patient-reported dyspnea (endpoint for which no differences were found in the main results of the trial), there was also no interaction between changes in the dyspnea visual analog scale area under the curve values and the 2 LVEF groups ($P = 0.830$ and $P = 0.636$ at 72 and 96 hours, respectively).

In terms of 24-hour urine volume, the overall results of the trial were significantly favorable for HCTZ, with a difference of 280 mL compared with placebo. When stratifying the results according to LVEF, a greater difference (555 mL) was found in patients with lower LVEF levels but, again, there was no interaction between LVEF and this outcome ($P = 0.481$).

On analyzing weight loss per 40 mg of furosemide, no significant interactions were observed in relation to the LVEF at either 72 or 96 hours ($P = 0.354$ and $P = 0.753$, respectively). Figure 2 presents these results graphically.

In the sensitivity analysis using the LVEF cutoff point of 50%, very similar results were obtained (Supplemental Table 2). Regarding the main primary endpoint (weight loss at 72 hours), a greater difference was again observed with HCTZ compared with placebo in patients with higher baseline LVEF values compared with lower LVEF values (difference of −1.15 [1.73 to 0.27] and −0.34 kg [−1.28 to 0.48], respectively), but, in this instance, the *P* value for the LVEF interaction was statistically significant ($P = 0.018$). For the rest of the primary and secondary efficacy variables, there was no significant interaction with the 2 LVEF groups.

TABLE 1 Baseline Characteristics According to LVEF on Admission

	LVEF ≤40% (n = 64)	LVEF >40% (n = 166)	*P* Value
Age, y	82.0 (76.8-86.0)	84.0 (78.0-88.0)	0.036
Female	17 (26.6)	94 (56.6)	<0.001
Systolic blood pressure, mm Hg	118 (110-130)	130 (114-144)	<0.001
Heart rate, beats/min	74.5 (68.8-88.0)	75.0 (65.0-86.8)	0.721
Baseline weight, kg	78.0 (63.4-85.5)	78.8 (69.0-90.6)	0.302
Body mass index kg/m^2	29.4 (25.4-32.3)	30.4 (26.6-34.6)	0.044
Medical history			
Hypertension	55 (85.9)	150 (90.4)	0.466
Diabetes	33 (51.6)	97 (58.4)	0.427
Atrial fibrillation or flutter	39 (60.9)	119 (71.7)	0.157
Anemia	24 (37.5)	79 (47.6)	0.218
Ischemic cardiomyopathy	32 (50.0)	43 (26.1)	0.001
Pacemaker	19 (29.7)	30 (18.1)	0.080
Stroke	8 (12.5)	23 (13.9)	0.957
COPD	19 (29.7)	33 (19.9)	0.156
Clinical features of HF			
NYHA functional class			
I	3 (4.69)	3 (1.82)	0.350
II	22 (34.4)	60 (36.4)	
III	35 (54.7)	82 (49.7)	
IV	4 (6.25)	20 (12.1)	
HF hospitalization within previous 12 mo	41 (64.1)	97 (58.4)	0.528
Emergency department HF-related visits within previous 12 mo	44 (68.8)	100 (60.2)	0.297
Analytical parameters			
Sodium, mmol/L	139 (136-141)	140 (137-142)	0.051
Potassium, mmol/L	4.16 (3.90-4.60)	4.30 (3.90-4.70)	0.402
Magnesium, mmol/L	2.01 (1.84-2.18)	2.03 (1.69-2.20)	0.624
Creatinine, mg/dL	1.42 (1.15-1.81)	1.40 (1.09-1.70)	0.234
eGFR, mL/min/1.73 m^2	44.2 (31.9-55.3)	43.5 (34.0-59.0)	0.952
BNP, pg/mL	1,702 (1,040-3,756)	645 (428-1766)	0.030
NT-proBNP, pg/mL	9,000 (4,943-14,969)	3,271 (1,922-7,784)	<0.001
Medications			
ACEI or ARB	32 (50.0)	95 (57.2)	0.401
Beta-blocker	42 (65.6)	97 (58.4)	0.396
MRA (25 mg/d)	31 (48.4)	50 (30.1)	0.014
Oral furosemide dose (mg/d)	80.0 (80.0-120)	80.0 (80.0-100)	0.063
Loop diuretic daily dose during treatment period			
Day 1 (randomization)	80 (80-120)	80 (80-120)	0.026
Day 2 (24 h after randomization)	80 (60-120)	80 (60-92.5)	0.033
Day 3 (48 h after randomization)	80 (60-120)	60 (40-80)	0.013
Day 4 (72 h after randomization)	80 (40-105)	60 (40-80)	0.043
Day 5 (96 h after randomization)	80 (40-120)	60 (40-80)	0.042

Value are median (IQR) or n (%).

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; BNP = B-type natriuretic peptide; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; HF = heart failure; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid-receptor antagonist; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

When evaluating LVEF as a continuous variable, the interaction analysis confirmed the absence of significant differences in treatment effect according to baseline LVEF. Figure 3 illustrates the treatment

TABLE 2 Treatment Effect for Primary and Secondary Efficacy Endpoints for the 2 Categorical Estimated LVEF Groups

	Results for Placebo	Results for HCTZ	Median Difference (95% CI)	*P* Value[a]
Primary endpoints				
Change in weight (kg) at 72 h				
Overall	−1.50 (−2.06 to −1.01)	−2.37 (−2.74 to −1.81)	−0.87 (−1.38 to −0.18)	0.001
≤40%	−1.82 (−2.26 to −0.92)	−2.14 (−2.86 to −1.38)	−0.32 (−1.56 to 0.54)	0.169
>40%	−1.39 (−2.02 to −0.92)	−2.48 (−2.93 to −1.83)	−1.09 (−1.56 to 0.43)	
AUC for dyspnea at 72 h (VAS scale)				
Overall	744 (645-1,046)	1,005 (773-1,161)	260 (−137 to 400)	0.878
≤40%	478 (244-1,318)	1,117 (717-1,520)	638 (−492 to 1,065)	0.830
>40%	763 (679-1,115)	990 (676-1,125)	227 (−206 to 380)	
Secondary endpoints				
Change in weight (kg) at 96 h				
Overall	−1.41 (−1.94 to −1.07)	−2.65 (−3.29 to −2.10)	−1.24 (−2.00 to −0.53)	<0.001
≤40%	−1.52 (−2.25 to −0.76)	−2.09 (−3.45 to −1.76)	−0.57 (−2.11 to −0.28)	0.663
>40%	−1.51 (−1.90 to −0.89)	−2.71 (−3.64 to −2.14)	−1.20 (−2.48 to −0.61)	
AUC for dyspnea at 96 h (VAS scale)				
Overall	1,282 (1,069-1,669)	1,610 (1,277-1,790)	327 (−144 to 587)	0.957
≤40%	1,021 (617-1,871)	1,534 (835-1,960)	513 (−223 to 1,128)	0.636
>40%	1,340 (1,147-1,975)	1,599 (1,212-1,877)	258 (−239 to 485)	
24-h diuresis quantification (mL)				
Overall	1,428 (1,366-1,559)	1,708 (1,544-1,927)	280 (99-503)	0.022
≤40%	1,402 (1,100-1,962)	1,957 (1,695-2,294)	555 (287-1,029)	0.481
>40%	1,490 (1,368-1,578)	1,629 (1,455-1,882)	139 (−33 to 456)	
Weight loss per 40 mg furosemide (from baseline to 72 h)				
Overall	−0.20 (−0.03 to −0.13)	−0.38 (−0.45 to −0.29)	−0.18 (−0.27 to −0.02)	0.001
≤40%	−0.17 (−0.36 to −0.10)	−0.26 (−0.54 to −0.20)	−0.09 (−0.37 to −0.06)	0.354
>40%	−0.19 (−0.31 to −0.13)	−0.39 (−0.46 to −0.30)	−0.20 (−0.27 to 0.02)	
Weight loss per 40 mg furosemide (from baseline to 96 h)				
Overall	−0.18 (−0.25 to −0.13)	−0.39 (−0.45 to −0.31)	−0.21 (−0.29 to −0.11)	<0.001
≤40%	−0.18 (−0.26 to −0.11)	−0.35 (−0.60 to −0.19)	−0.16 (−0.32 to −0.05)	0.753
>40%	−0.17 (−0.27 to −0.10)	−0.42 (−0.46 to −0.30)	−0.25 (−0.33 to 0.11)	
Net fluid loss (mL) per 40 mg of furosemide (from baseline to 72 h)				
Overall	726 (660-799)	799 (739-879)	72 (0.16-171)	0.154
≤40%	656 (531-783)	803 (699-864)	147 (48-284)	0.441
>40%	768 (676-848)	801 (742-913)	33 (−50 to 190)	

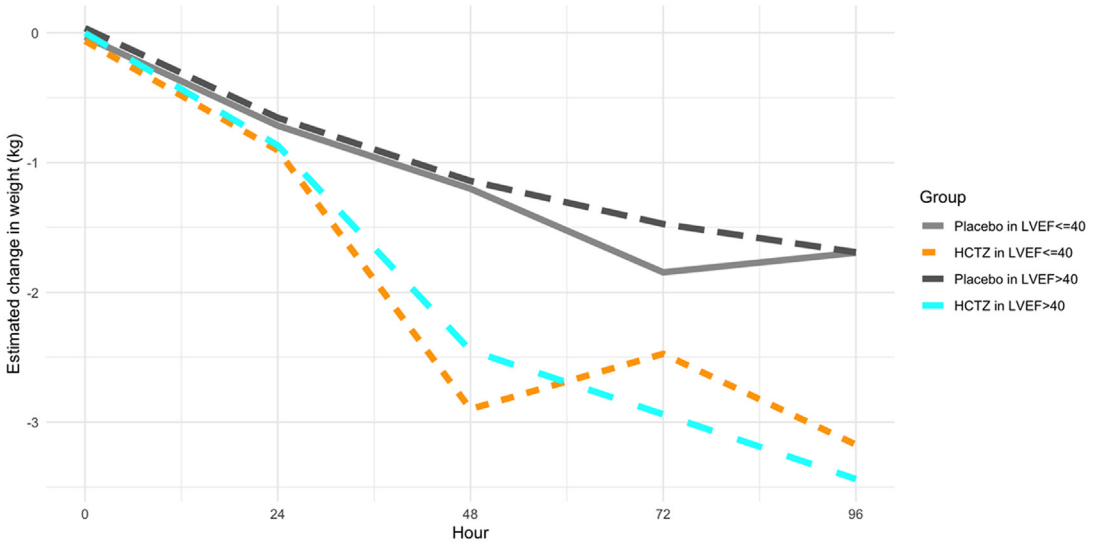
[a]For each outcome, the first *P* value assesses the adjusted median difference between hydrochlorothiazide (HCTZ) and placebo on the analyzed outcome by comparing the model with it and adjusted by the weight and the set of unbalanced variables at baseline with the model without treatment. Equivalently, the second *P* value assesses the adjusted interaction effect between the treatment and left ventricular ejection fraction (LVEF) groups on the analyzed outcome by comparing the model with it and their main effects and adjusted by the same variables with the model without this interaction. 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.

AUC = area under the curve; VAS = visual analog scale.

effect of HCTZ on weight changes at 72 ($P = 0.318$) and 96 ($P = 0.583$) hours, visualized as a restricted cubic spline across the entire LVEF range. This continuous quantitative analysis also found no significant interactions of LVEF on the other primary and secondary efficacy endpoints (Supplemental Figures 1 and 2).

EFFECT OF LVEF 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 2 treatment groups (HCTZ vs placebo).[7] In this post hoc stratified analysis, *P* values for the LVEF

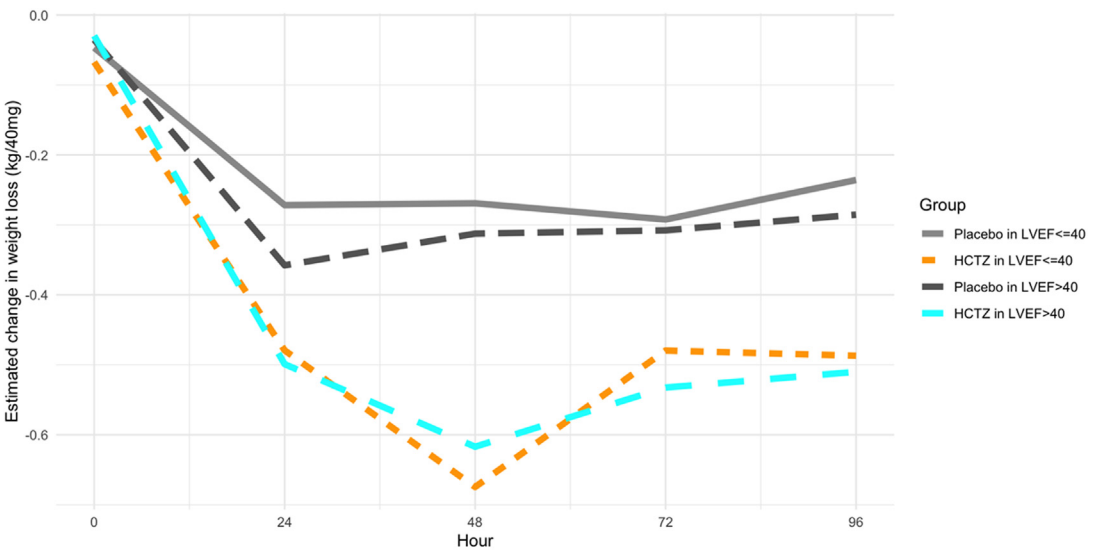
FIGURE 1 **Changes in Weight in the 2 Treatment Arms and 2 LVEF Groups**



Adjusted changes in weight at 72 and 96 hours after randomization in the 2 treatment arms (hydrochlorothiazide [HCTZ] or placebo) and the 2 left ventricular ejection fraction (LVEF) groups.

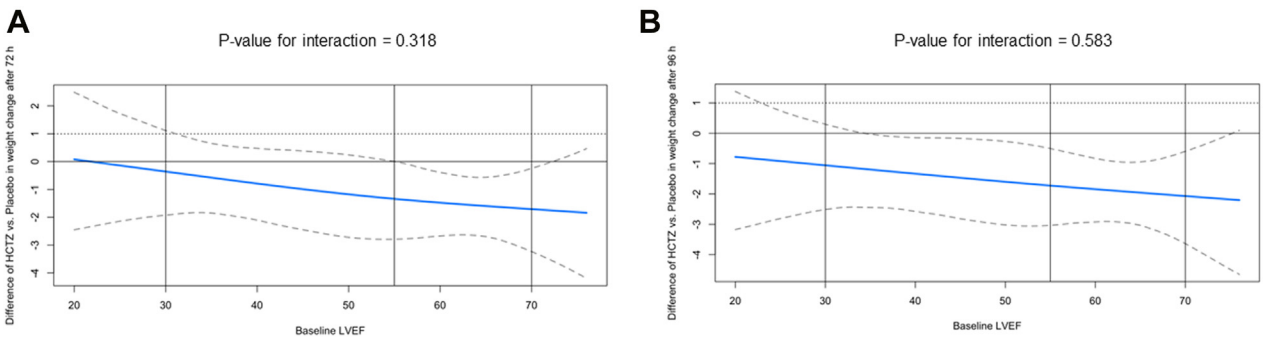
interaction terms were not significant for 30- and 90-day mortality ($P = 0.129$ and $P = 0.251$, respectively) or for 30- and 90-day all-cause rehospitalizations ($P = 0.451$ and $P = 0.960$, respectively). Using the LVEF cutoff point of 50%, we found no significant interaction between these secondary endpoints and the 2 LVEF groups. The results of the treatment effect on mortality and rehospitalizations stratified according to LVEF are shown in **Table 3** and Supplemental Table 3.

FIGURE 2 **Changes in Weight per mg of Furosemide in the 2 Treatment Arms and 2 LVEF Groups**



Metric of diuretic response (changes in weight per 40 mg of furosemide) at 72 and 96 hours after randomization for the 2 treatment arms (HCTZ or placebo) and the 2 LVEF groups (cutoff LVEF >40% vs LVEF ≥40%). Abbreviations as in **Figure 1**.

FIGURE 3 Changes in Weight According to LVEF as a Continuous Variable



Restricted cubic spline curves showing differences in weight at 72 hours (A) and 96 hours (B) according to LVEF as a continuous variable (cutoff LVEF >40% vs LVEF ≥40%). Abbreviations as in Figure 1.

EFFECT OF LVEF ON THE TREATMENT EFFECT FOR SAFETY ENDPOINTS. The main results of the CLOROTIC trial found that patients randomized into the HCTZ arm more frequently experienced worsening renal function,[7] but significant differences in this endpoint were not observed in the 2 LVEF groups in this post hoc analysis ($P = 0.185$).

Regarding hyponatremia and hypokalemia, the results were also similar for the different cutoff 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 main trial results or when stratified according to LVEF (Table 3).

Finally, there were no significant differences in hyperkalemia (defined as potassium levels >5.0 mmol/L), the prevalence of which was similar between the 2 groups in the main trial (22.4% and 21.9% in those assigned to placebo and HCTZ, respectively) and among the 2 LVEF groups ($P = 0.859$).

Again, using the LVEF cutoff point of 50%, we found no significant interaction between any safety endpoints and the 2 LVEF groups (Supplemental Table 3).

DISCUSSION

This post hoc analysis of the CLOROTIC trial assessed patients' diuretic response to combined diuretics (oral HCTZ and intravenous loop diuretics) across the LVEF spectrum. The primary conclusion of this study is that LVEF did not significantly modify the efficacy of this combined diuretic strategy in AHF. In other words, the addition of HCTZ to furosemide was associated with an improvement in diuretic response across the entire LVEF spectrum.

As expected, some differences were observed in baseline characteristics of patients with lower vs higher LVEF values. However, less than one-third of the patients in the CLOROTIC trial had HFrEF and, thus, the study was perhaps more representative of patients with HFmrEF and HFpEF. This lower representation of HFrEF can be explained, in part, by the fact that in Spain, Internal Medicine Departments provide care to a greater percentage of patients with HFpEF compared with Cardiology Departments, which usually provide care to more patients with HFrEF.[13,14] Nevertheless, another small, single-center clinical trial randomized 51 patients with AHF to receive oral HCTZ or a placebo for 3 days.[15] This study was more representative of HFrEF, as only patients with LVEF ≤45% were enrolled, and the results were very similar to those of the CLOROTIC trial.

HF guidelines recommend using diuretics to relieve congestion,[16] but few clinical trials have tested the use of different diuretic agents, especially combinations of diuretic agents added to loop diuretics. One study that has analyzed this aspect is the ADVOR (Acetazolamide in Decompensated Heart Failure with Volume Overload) trial, which showed that acetazolamide added to intravenous loop diuretics was associated with a greater proportion of patients without residual signs of congestion after 3 days of treatment and without a greater risk of adverse events compared with high-dose intravenous loop diuretics alone.[9] The possibility of treatment effect modification according to baseline LVEF for patients enrolled in the ADVOR trial was also analyzed in a prespecified subanalysis; there was no statistically significant treatment effect modification according to baseline

LVEF on the treatment effect of acetazolamide for different decongestion endpoints. The doubling of creatinine (a predefined safety endpoint of the ADVOR trial) was not more frequent in patients randomized into the acetazolamide arm. However, in the LVEF subanalysis, patients treated with acetazolamide had statistically significant increases in creatinine during the treatment phase, and this increase was more pronounced in patients with HFrEF.[17]

The CLOROTIC trial showed improved diuretic response with combined treatment in patients with AHF, and a recent subanalysis showed that this effect occurred regardless of baseline eGFR, although the effects tended to be more pronounced in patients with higher eGFR values.[18] However, it was unknown if baseline LVEF could have influenced the efficacy and safety endpoints of the trial.

This post hoc analysis found that the addition of HCTZ to furosemide in patients with AHF improved the diuretic response without significant differences across the LVEF spectrum. The main results of the CLOROTIC trial did not show a significant improvement in patient-reported dyspnea in patients treated with HCTZ. This post hoc analysis also did not observe an improvement in dyspnea in any of the LVEF groups. This lack of improvement in patient-reported dyspnea may be explained by the fact that patient-assessed dyspnea is only modestly correlated with more objective physician-assessed changes in signs of HF; many patients with AHF are admitted due to worsening peripheral edema and dyspnea on exertion but do not have resting dyspnea, and if resting dyspnea is not present, it logically cannot improve; and finally, changes in dyspnea on exertion may also be underestimated in the hospital setting, where patients are typically less active.[19]

Regarding safety endpoints, there were no significant differences in any of the prespecified safety outcomes when stratifying patients according to LVEF. In the overall results of the CLOROTIC trial, worsening renal function and hypokalemia (using 3.5 and 3.0 mmol/L as cutoff values) were significantly more common in patients assigned to receive HCTZ. No significant interactions were found for these safety endpoints according to LVEF in this post hoc analysis.

Both strategies, combining acetazolamide or combining HCTZ with loop diuretics, seem to be efficacious for improving congestion in AHF regardless of baseline LVEF or eGFR.[17,18,20] This has led to debate about which diuretic should be the agent of choice when combining diuretics.[21]

The recently published PUSH-AHF (Pragmatic Urinary Sodium-based Treatment Algorithm in

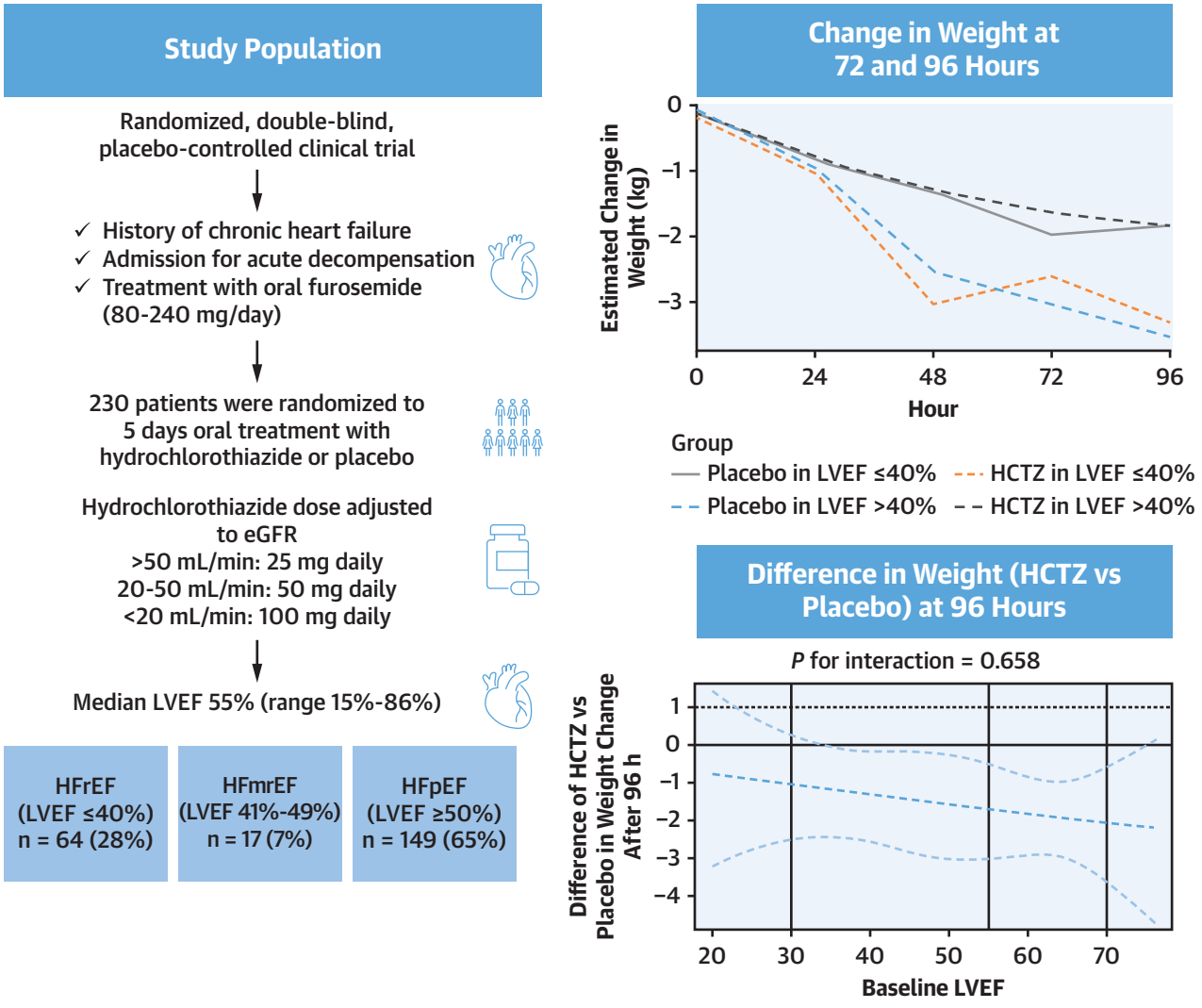
TABLE 3 Treatment Effect for Mortality, Rehospitalizations and Safety Endpoints for the 2 Categorical LVEF groups

	Results for Placebo	Results for HCTZ	Model Estimated Effect	
			HR (95% CI)	*P* Value[a]
Secondary endpoints				
All-cause mortality at 30 d				
Overall	7/116	11/114	1.57 (0.59-4.17)	0.358
≤40%	4/29	3/35	0.56 (0.10-3.19)	0.129
>40%	3/87	8/79	2.89 (0.76-10.96)	
All-cause mortality at 90 d				
Overall	19/116	23/114	1.24 (0.67-2.28)	0.487
≤40%	7/29	6/35	0.72 (0.23-2.19)	0.251
>40%	12/87	17/79	1.57 (0.7 -3.30)	
All-cause rehospitalizations at 30 d				
Overall	18/116	27/114	1.63 (0.9-2.97)	0.104
≤40%	4/29	5/35	1.06 (0.28-3.97)	0.451
>40%	14/87	62/79	1.88 (0.96-3.68)	
All-cause rehospitalizations at 90 d				
Overall	39/116	43/114	1.25 (0.81-1.94)	0.307
≤40%	6/29	9/35	1.29 (0.46-3.63)	0.960
>40%	33/87	34/79	1.32 (0.82-2.15)	
			OR (95% CI)	
Safety endpoints				
Impaired renal function (increase in creatinine levels >26.5 μmol/L)				
Overall	20/116	53/114	4.16 (2.30-7.78)	<0.001
≤40%	9/29	18/35	2.31 (0.83-6.67)	0.185
>40%	11/87	35/79	5.54 (2.62-12.5)	
Hyponatremia (sodium level ≤130 mmoL/L)				
Overall	6/116	10/114	1.73 (0.62-5.25)	0.299
≤40%	1/29	1/35	0.78 (0.03-20.42)	0.527
>40%	5/87	9/79	2.11 (0.69-7.17)	
Hyponatremia (sodium level ≤125 mmoL/L)				
Overall	2/116	3/114	1.4 (0.22-11.1)	0.721
≤40%	0/29	0/35	Nonestimable value	1.000
>40%	2/87	3/79	1.43 (0.22-11.49)	
Hypokalemia (potassium levels ≤3.5 mmoL/L)				
Overall	22/116	51/114	3.44 (1.92-6.34)	<0.001
≤40%	7/29	17/35	3.10 (1.08-9.65)	0.838
>40%	15/87	34/79	3.55 (1.76-7.41)	
Hypokalemia (potassium levels ≤3.0 mmoL/L)				
Overall	3/116	13/114	4.75 (1.47-21.21)	0.008
≤40%	1/29	7/35	7.43 (1.19-144.94)	0.551
>40%	2/87	6/79	3.30 (0.73-23.10)	
Hypokalemia (potassium levels ≤2.5 mmoL/L)				
Overall	0/116	2/114	Nonestimable value	0.098
≤40%	0/60	0/35	Nonestimable value	1.000
>40%	0/87	2/79	Nonestimable value	

[a]For each outcome, the first *P* value assesses the adjusted median difference between HCTZ and placebo on the analyzed 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 LVEF groups on the analyzed outcome by comparing the model with it and their main effects and adjusted by the same variables with the model without this interaction. Safety endpoints captured any event observed at any time throughout the study.

Abbreviations as in Table 2.

CENTRAL ILLUSTRATION The CLOROTIC Trial Results According to LVEF



Adding oral HCTZ to intravenous furosemide improved the diuretic response in patients admitted due to AHF without treatment effect modification by baseline LVEF

Sánchez-Marteles M, et al. J Am Coll Cardiol HF. 2024;■(■):■-■.

Adding oral hydrochlorothiazide (HCTZ) to intravenous furosemide improved the diuretic response in patients admitted to acute heart failure (AHF) without treatment affect modification by baseline left ventricular ejection fraction (LVEF). CLOROTIC = Combining Loop with Thiazide Diuretics for Decompensated Heart Failure; eGFR = estimated glomerular filtration rate; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction.

Acute Heart Failure) trial illustrates the feasibility of using a urinary sodium-guided approach for dosing loop diuretics.[4] This trial showed that such an intervention helps to optimize loop diuretic doses, increasing natriuresis and diuresis without inducing significant changes in eGFR. Urinary sodium-guided decongestion can be helpful during decongestion, perhaps ultimately limiting the need for combined diuretics. If true diuretic resistance is present despite optimization of loop diuretics, a combined diuretic approach should be considered, and HCTZ might be preferential in patients who receive chronic high doses of loop diuretics.[3]

Accordingly, it can be concluded that the universal feature of congestion may be improved with acetazolamide or HCTZ, despite known pathophysiological and baseline differences in the subtypes of HF according to LVEF.

STUDY LIMITATIONS. First, this study was a post hoc analysis of the CLOROTIC trial, which was only powered to test the treatment effect in the total study cohort. The statistical power of our analyses was low given the small size of the trial. Second, the echocardiographic assessment of LVEF is subject to interobserver and temporal variability, particularly when performed locally by the study sites. Third, LVEF was reported by site investigators and not by a central echocardiogram laboratory. Fourth, there were few patients with HFmrEF, and it was therefore not possible to perform a comparative analysis with the 3 HF categories defined according to European Society of Cardiology HF guidelines. Instead, the comparison was made by using 2 groups with an LVEF cutoff point of 40% (and a sensitivity analysis using a higher cutoff value of 50%). Besides, the additional approach of analyzing LVEF on a continuous scale reduces the potential misclassification of LVEF compared with using a categorical classification approach alone.

CONCLUSIONS

Adding HCTZ to intravenous furosemide seems to be an effective strategy for improving diuretic response in patients with AHF without treatment effect modification according to baseline LVEF (**Central Illustration**).

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ADDRESS FOR CORRESPONDENCE: Dr Marta Sánchez-Marteles, Internal Medicine Department, Hospital Clínico Universitario "Lozano Blesa," Calle de San Juan Bosco, 15, 50009 Zaragoza, Spain. E-mail: marta.sanchez15@yahoo.es. X: @msanchezmar.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE AND PATIENT CARE AND PROCEDURAL SKILLS: In this post hoc analysis of the CLOROTIC clinical trial which analyzed 230 patients with AHF, HCTZ significantly increased diuretic response in patients with HF classified into different subtypes according to LVEF compared with placebo. In addition, there were no significant differences in any of the prespecified safety endpoints upon stratifying the analysis according to LVEF.

TRANSLATIONAL OUTLOOK: Despite known pathophysiological and baseline differences in patients with HF classified into various subtypes according to LVEF, combining loop diuretics with HCTZ may be beneficial for the universal feature of congestion.

REFERENCES

1. Groenewegen A, Rutten FH, Mosterd A, Hoes AW. Epidemiology of heart failure. *Eur J Heart Fail*. 2020;22(8):1342-1356.

2. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42(36):3599-3726.

3. Martens P, Mullens W. Using combinational diuretics across the spectrum of renal function. *Eur J Heart Fail*. 2023;25(10):1794-1796.

4. Ter Maaten JM, Beldhuis IE, van der Meer P, et al. Natriuresis-guided diuretic therapy in acute heart failure: a pragmatic randomized trial. *Nat Med*. 2023;29(10):2625-2632.

5. Mullens W, Damman K, Harjola VP, et al. The use of diuretics in heart failure with congestion—a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2019;21(2):137-155.

6. Dimond MG, Ibrahim NE, Fiuzat M, et al. Left ventricular ejection fraction and the future of heart failure phenotyping. *J Am Coll Cardiol HF*. 2024;12(3):451-460.

7. Greene SJ, Bauersachs J, Brugts JJ, et al. Management of worsening heart failure with reduced ejection fraction: JACC Focus Seminar 3/3. *J Am Coll Cardiol*. 2023;82(6):559-571.

8. Lewis GA, Schelbert EB, Williams SG, et al. Biological phenotypes of heart failure with preserved ejection fraction. *J Am Coll Cardiol*. 2017;70(17):2186-2200.

9. Mullens W, Dauw J, Martens P, et al. Acetazolamide in acute decompensated heart failure with volume overload. *N Engl J Med*. 2022;387(13):1185-1195.

10. Trullàs JC, Morales-Rull JL, Casado J, et al. Combining loop with thiazide diuretics for decompensated heart failure: the CLOROTIC trial. *Eur Heart J*. 2023;44(5):411-421.

11. Trullàs JC, Morales-Rull JL, Casado J, Freitas Ramírez A, Manzano L, Formiga F. Rationale and design of the "Safety and Efficacy of the Combination of Loop with Thiazide-type Diuretics in Patients with Decompensated Heart Failure (CLOROTIC) Trial": a double-blind, randomized, placebo-controlled study to determine the effect of combined diuretic therapy (loop diuretics with thiazide-type diuretics) among patients with decompensated heart failure. *J Card Fail*. 2016;22(7):529-536.

12. Felker GM, Lee LK, Bull DA, et al. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med*. 2011;364:797-805.

13. Álvarez-García J, Salamanca-Bautista P, Ferrero-Gregori A, et al. Prognostic impact of physician specialty on the prognosis of outpatients with heart failure: propensity matched analysis of the REDINSCOR and RICA registries. *Rev Esp Cardiol (Engl Ed)*. 2017;70(5):347-354.

14. Trullàs JC, Pérez-Calvo JI, Conde-Martel A, et al. Epidemiology of heart failure with preserved ejection fraction: results from the RICA Registry on behalf of researchers from the RICA Registry 1. *Med Clin*. 2021;157(1):1-9.

15. Piardi DS, Butzke M, Mazzuca ACM, et al. Effect of adding hydrochlorothiazide to usual treatment of patients with acute decompensated heart failure: a randomized clinical trial. *Sci Rep*. 2021;11(1):16474.

16. McDonagh TA, Metra M, Adamo M, et al. 2023 Focused update of the 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2023;44(37):3627-3639.

17. Martens P, Dauw J, Verbrugge FH, et al. Decongestion with acetazolamide in acute decompensated heart failure across the spectrum of left ventricular ejection fraction: a prespecified analysis from the ADVOR Trial. *Circulation*. 2023;147(3):201-211.

18. Trullàs JC, Morales-Rull JL, Casado J, et al. Combining loop and thiazide diuretics for acute heart failure across the estimated glomerular filtration rate spectrum: a post-hoc analysis of the CLOROTIC trial. *Eur J Heart Fail*. 2023;25(10):1784-1793.

19. Zakeri R, Wilson DG, Mohammed SF. Time to revisit combination loop and thiazide diuretic therapy for patients with acute heart failure. *Eur Heart J*. 2023;44(5):422-424.

20. Meekers E, Dauw J, Packer M, et al. Renal function and decongestion with acetazolamide in acute decompensated heart failure: the ADVOR trial. *Eur Heart J*. 2023;44(37):3672-3682.

21. Mullens W, Schulze PC, Westphal J, Bogoviku J, Bauersachs J. Great debate: in patients with decompensated heart failure, acetazolamide in addition to loop diuretics is the first choice. *Eur Heart J*. 2023;44(24):2159-2169.

KEY WORDS acute heart failure, diuretics, hydrochlorothiazide, left ventricular ejection fraction, thiazides

APPENDIX For supplemental figures and tables, please see the online version of this paper.