of the platform and the possibility of repositioning and recapturing the device until 90% of the valve has been released.

Conduction disturbances continue to be the Achilles heel of most self-expanding valves.[1] In this regard, although our patient developed complete atrioventricular block, it is still early to draw conclusions. The possibility of recapturing and repositioning the prosthesis could minimize the risk of electrical disturbances, perivalvular leaks, mitral valve involvement, and coronary occlusion.

The initial experience with the self-expanding Vienna valve in the VIVA study seeks to demonstrate the short-term safety and effectiveness in order to obtain CE mark approval. Its innovative precrimped system may reduce both procedural time (essential in emergent scenarios) and costs, while maintaining an adequate radial strength and navigability. Studies with longer-term follow-up will undoubtedly be necessary to determine the durability of leaflets treated with this particular method.[2]

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AUTHORS' CONTRIBUTIONS

Dr Amat-Santos contributed to the study design. J.C. Gonzalez-Gutiérrez, S. Blasco-Turrión, A. Campo, and J.P. Sánchez-Luna collected and analyzed the information. All authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

The institution participates in the VIVA trial and receives research grants from Products & Features. I.J. Amat-Santos is proctor for Products & Features.

APPENDIX. SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version, at https://doi.org/10.1016/j.rec.2022.10.008

José Carlos González-Gutiérrez,[a] Sara Blasco-Turrión,[a] Alberto Campo-Prieto,[a,b] Juan Pablo Sánchez-Luna,[a] J. Alberto San Román,[a,b] and Ignacio J. Amat-Santos[a,b,*]

[a]*Departamento de Cardiología, Hospital Clínico Universitario de Valladolid, Valladolid, Spain*
[b]*Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Spain*

[*] Corresponding author.
E-mail address: ijamat@gmail.com (I.J. Amat-Santos).

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CANDI study: chlorthalidone vs acetazolamide in patients with diuretic resistance in acute heart failure

CANDI: clortalidona frente a acetazolamida en pacientes con resistencia diurética e insuficiencia cardiaca aguda

To the Editor,

Diuretic resistance is a common problem during hospitalization and is associated with increased mortality and risk of rehospitalization.[1] European Guidelines recommend a second diuretic when an adequate diuretic response is not achieved with loop diuretics.[2] It remains unclear which combination therapy is the most effective.[2] We aimed to evaluate the early effect and safety of chlorthalidone and acetazolamide in a cohort of patients with acute heart failure (AHF). We performed an observational, retrospective, single-center study of AHF patients and poor diuretic response defined as persistent congestion assessed by the composite congestion score and no loss of at least 1 kg the previous day. Acetazolamide or chlorthalidone was added at the discretion of the treating physician. Vital signs, body weight, and diuresis on "day 0" (before the administration of the second diuretic) and on "day 1" (24 hours after) were recorded. Urine and blood tests were obtained. As endpoints, we evaluated the proportion of patients with loss of at least 1 kg 24 hours after the second diuretic, as this was a common clinical target of successful decongestion in our clinical practice. Other endpoints were changes in weight, urinary output, natriuresis, and renal and electrolyte variations.

Continuous variables are presented as the median [interquartile range]. Categorical variables are described as absolute and relative frequencies. Comparison of clinical characteristics was analyzed by the chi-square test for categorical variables and the Mann-Whitney U test for continuous variables. Inverse-probability-weighted (IPW) regression adjustment analysis was performed to estimate the average treatment effect (ATE) of the second diuretic administration on weight loss $>$ 1 kg. We obtained the propensity to receive either chlorthalidone or acetazolamide based on sex, chronic kidney disease, pulmonary disease, left and right ventricular dysfunction, and baseline creatinine. Second diuretic administration ATE was estimated based on the IPW and the baseline weight, baseline glomerular filtration rate, systolic blood pressure, and natriuresis. Differences in diuresis and natriuresis were assessed through an ANCOVA approach, adjusting for the same above-mentioned parameters, showing the effect size and the corresponding 95%. A 2-tailed P value $<$ .05 was considered significant.

The present study conforms to the principles of the Declaration of Helsinki. Approval from the local ethics committee/internal review board was obtained and patients signed informed consent forms.

From November 2019 to March 2022, 55 patients were included. The baseline characteristics are presented in Table 1. Twenty-six patients (47.3%) were treated with acetazolamide

Table 1
Baseline characteristics, treatment, parameters on day 0 and day 1, length of stay and events during admission

	Total (n = 55)	Acetazolamide group (n = 26)	Chlorthalidone group (n = 29)	*P*
Baseline characteristics				
Female sex	19 (34.5)	6 (23.1)	13 (44.8)	.090
Age, y	77 [73-82]	77 [74.5-81.8]	77 [71.4-82.5]	.710
Hypertension	45 (81.8)	23 (88.5)	22 (75.9)	.226
Diabetes mellitus	19 (34.5)	8 (30.8)	11 (37.9)	.577
History of atrial fibrillation	45 (81.8)	21 (80.8)	24 (82.8)	.849
Coronary artery disease	19 (34.5)	10 (38.5)	9 (31)	.563
Chronic kidney disease (stage ≤ 3A)	22 (40)	13 (50)	9 (31)	.152
Pulmonary disease	18 (32.7)	6 (23.1)	12 (41.4)	.149
Previous hospitalization for heart failure in last year	19 (34.5)	8 (30.8)	11 (37.9)	.577
Ambulatory treatment				
Furosemide	43 (78.2)	21 (80.8)	22 (75.9)	.660
Furosemide dose, mg/24 h	80 [20-120]	70 [20-120]	80 [5-180]	.475
Chlorthalidone	12 (21.8)	6 (23.1)	6 (20.7)	.831
Acetazolamide	0 (0)	0 (0)	0 (0)	-
Spironolactone	15 (27.3)	9 (34.6)	6 (20.7)	.247
Echocardiogram at admission				
Preserved LVEF	30 (54.5)	13 (50)	17 (58.6)	.522
Severe LVEF dysfunction	14 (25.5)	9 (34.6)	5 (17.2)	.140
Right ventricular dysfunction	21 (38.2)	12 (46.2)	9 (31)	.249
Tricuspid regurgitation III-IV	17 (30.9)	10 (38.5)	7 (24.1)	.211
Systolic pulmonary artery pressure, mmHg	45 [40-55]	45 [36 –55]	50 [45-60]	.322
Parameters at day 0				
NT-proBNP, pg/mL	3260 [1520-6824]	2671 [1273-8046]	3552 [1599-6475]	.696
Maximum furosemide dose during admission, mg/24h	120 [120-250]	120 [120-250]	120 [120-240]	.203
Concomitant furosemide dose, mg/24 h	120 [120-180]	120 [110-250]	120 [120-160]	.475
Concomitant hypertonic saline	11 (20)	7 (26.9)	4 (13.8)	.224
Concomitant inotropes	2 (3.6)	2 (7.7)	0 (0)	.128
Systolic blood pressure, mmHg	117 [102-128]	118 [99-128]	113 [104-130]	.642
Diastolic blood pressure, mmHg	65 [58-75]	66 [55-73]	65 [58-77]	.879
Venous blood pH	7.41 [7.36-7.44]	7.42 [7.39-7.45]	7.38 [7.35-7.43]	.084
Bicarbonate levels, mEq/L	28 [25.6-31]	28 [25.9-31.3]	28 [25.5-29.8]	.545
pCO_2 levels, mmHg	47.3 [43.5-54.4]	46.6 [43-51.6]	50.6 [42.8-55.4]	.411
GFR, mL/min/1.73 m^2	51 [34-68]	44 [31-65]	52 [38-79]	.169
Creatinine levels, mg/dl	1.29 [0.98-1.70]	1.36 [1.05-2.09]	1.25 [0.86-1.49]	.067
Serum potassium levels, mEq/L	3.9 [3.6-4.4]	3.8 [3.5-4.0]	4.1 [3.6-4.5]	.018
Serum sodium levels, mEq/L	141 [138-143]	141 [137-143]	140 [138-143.5]	.542
Urinary sodium, mEq/L	43.5 [27-77.5]	43 [28.2-79.0]	44 [26.5-75.5]	.658
Parameters and endpoints on day 1				
Concomitant furosemide dose, mg/24 h	120 [120-180]	120 [110-250]	120 [120-160]	.475
Change in systolic blood pressure, mmHg	+0 [−7-8]	− 1 [10-4]	-0 [−6-10]	.426
Change in diastolic blood pressure, mmHg	+0 [−9-5]	− 2 [−9.8-3.8]	+1 [−9-6]	.416
Change in venous blood pH	+0 [−004-0.03]	− 0.01 [−0.05-0.00]	+0.02 [+0-0.06]	.002
Change in bicarbonate levels, mEq/L	− 0.85 [−2.3-1.2]	− 1.8 [-2.9 to − 0.5]	+0.02 [−1.1-2.3]	.013

Table 1 *(Continued)*
Baseline characteristics, treatment, parameters on day 0 and day 1, length of stay and events during admission

	Total (n = 55)	Acetazolamide group (n = 26)	Chlorthalidone group (n = 29)	*P*
Change in pCO_2 levels, mmHg	− 1.1 [−5.1-1.8]	− 0.1 [-3.4-+2.3]	− 4.3 [−6.1 to − 0.7]	.102
Change in GFR, mL/min/1.73 m^2	+1 [−5-6]	+0 [−3 to +6]	+2 [−6 to +6]	.866
Change in creatinine levels, mEq/L	+0.03 [−0.07-0.13]	+0.02 [−0.06-0.14]	+0.03 [−0.12-0.12]	.607
Change in serum potassium levels, mEq/L	− 0.1 [−0.3-0.2]	− 0.1 [−0.3-0.0]	− 0.0 [−0.3-0.4]	.360
Change in serum sodium, mEq/L	+0 [−2-1]	+0.5 [−1.3-1]	− 1 [−2.5-2]	.682
Weight loss ≥ 1 kg	23 (41.8)	15 (57.7)	8 (27.6)	.024
Change in weight, kg	− 0.65 [−1.40-0]	− 1.1 [−1.5 to − 0.3]	− 0.3 [−1-0.1]	.047
Change in diuresis, mL	+200 [−143-648]	+285 [−78-630]	+80 [−225-657]	.517
Change in natriuresis, mEq/L	+14.5 [−6.25-46.8]	+23 [−6.3-53.9]	+13 [−6.3-24.5]	.296
Events during admission				
Length of stay after second diuretic drug, d	10 [4-19]	11 [4-21]	7 [4-17]	.306
Death during admission	3 (5.5)	2 (7.7)	1 (3.4)	.489

GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide.
The data are expressed as No. (%) or median [interquartile range].

(median dose: 125 [125-250] mg) and 29 (52.7%) with chlorthalidone (median dose: 25 [25-25] mg). The median maximum dose of furosemide during admission was 125 [120-250] mg. Combination therapy was started on the 7th day of admission (acetazolamide on the 7th [4-11 day], chlorthalidone on the 7th [5-10] day; *P* = .793), with a concomitant median furosemide dose of 120 [120-180] mg. Patients who received acetazolamide had lower baseline serum potassium levels.

Overall, 41.8% of the patients lost at least 1 kg after the association of a second diuretic. After adjustment through the IPW, the average treatment effect of acetazolamide vs chlorthalidone was 0.36 (95% confidence interval [95%CI], 0.09-0.63, *P* = .008). The estimated potential-outcome mean of losing ≥ 1 kg in the patients who received acetazolamide was 62% (95%CI, 39-84) and 26% (95%CI, 10-41) for those receiving chlorthalidone.

There were no significant differences in diuresis (effect size of acetazolamide: + 202.5 mL, 95%CI, − 155.1-560.1; *P* = .260) and natriuresis (effect size of acetazolamide: + 13.11 mEq/l (95%CI, − 2.35-28.59, *P* = .095).

The use of acetazolamide was associated with a greater decrease in pH and bicarbonate levels, but the magnitude of the difference was low.

To date, there are no valuable parameters to predict in-hospital diuretic resistance beyond urinary sodium after the first diuretic administration,[3] but the value of natriuresis after several days remains unclear.[3] It is important to note that our patients received the coadjuvant diuretic on the 7th day of admission.

On the other hand, although weight change may be influenced by water-food intake, its measurement is commonly used to monitor response to diuretic therapy. Several studies have shown that a poor diuretic response assessed by weight is associated with a worse prognosis.[1] In clinical practice, the goal of a daily loss of 1 kg while congestion persists seems reasonable.

European Guidelines recommend a combined diuretic strategy based on sequential nephron blockade, suggesting thiazides as the first-line treatment and acetazolamide as second-line.[2] These recommendations were based on their pathophysiological mechanisms and observational studies. Two randomized, placebo-controlled trials, CLOROTIC[4] and ADVOR,[5] have recently shown the efficacy of hydrochlorothiazide and acetazolamide, respectively, in obtaining successful decongestion when added to a loop diuretic. To date, no randomized trials have compared the use of oral thiazides with acetazolamide in combination with loop diuretics.[2] To our knowledge, the CANDI trial is the first to evaluate the early effect of oral acetazolamide and chlorthalidone on top of loop diuretics in patients admitted for AHF with diuretic resistance. With the limitations of a single-center, observational study, we found that compared to chlorthalidone, acetazolamide was associated with a higher proportion of patients with 24-hour weight loss of at least 1 kg with a neutral effect on 24-hour diuresis and natriuresis.

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AUTHORS' CONTRIBUTIONS

M. Cobo Marcos contributed to the conception and design of the study. D. Sánchez Ortiz and A. Matutano Muñoz contributed to patient inclusion. P. Vela Martín contributed to data inclusion in the database. P. Vela Martín organized the database. A. Royuela performed the statistical analysis. P. Vela Martín, M. Cobo Marcos and F. Domínguez wrote the first draft of the manuscript. All authors contributed to manuscript revision, and have read and approved the submitted version

CONFLICTS OF INTERESTS

None.

Paula Vela Martín,[a] Andrea Matutano Muñoz,[a] David Sánchez Ortiz,[a] Fernando Domínguez,[a,b,c] Ana Royuela,[d,e] and Marta Cobo Marcos[a,c,*]

[a]*Departamento de Cardiología, Hospital Universitario Puerta de Hierro Majadahonda, Instituto Investigación Sanitaria Puerta de Hierro (IDIPHISA), Majadahonda, Madrid, Spain*
[b]*Grupo de Miocardiopatías Hereditarias, Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain*
[c]*Centro de Investigación Biomédica en Red en Enfermedades Cardiovasculares (CIBERCV), Spain*
[d]*Unidad de Bioestadística, Hospital Universitario Puerta de Hierro Majadahonda, Instituto Investigación Sanitaria Puerta de Hierro (IDIPHISA), Madrid, Spain*
[e]*Centro de Investigación Biomédica en Red Epidemiología y Salud Pública (CIBERESP), Spain*

* Corresponding author.
E-mail address: martacobomarcos@hotmail.com (M. Cobo Marcos).

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Treatment of mild asymptomatic cardiotoxicity in early-stage HER 2-positive breast cancer. Is it justified?

Tratamiento de la cardiotoxicidad leve asintomática en cáncer de mama HER2 positivo precoz. ¿Está realmente justificado?

To the Editor,

The definition of cancer therapy-related cardiac dysfunction (CTRCD) has changed in recent years. At present, CTRCD is classified as mild when troponin is elevated or when there is > 15% change in global longitudinal strain (GLS) from baseline with left ventricular ejection fraction (LVEF) ≥ 50%, moderate when LVEF drops 10 points and is 40% to 49%, and severe when LVEF drops below 40%.[1] The recently published Guidelines on Cardio-Oncology[2] recommend starting beta-blockers and angiotensin-converting enzyme inhibitors (ACEIs) in cases of mild CTRCD to prevent progression to moderate-to-severe CTRCD, as a class IIa recommendation with level of evidence B.[2]

In this study, the incidence of CTRCD was measured in a cohort of patients with early HER2-positive breast cancer (eHER2-bc). Likewise, the study investigated the predictive value of high-sensitivity troponin I (hsTnI) and GLS for the appearance of moderate-to-severe CTRCD, as well as their potential as tools to aid in the decision to start cardioprotective treatment.

Between May 2018 and May 2021, 95 consecutive patients with eHER2-bc were enrolled in the study at a tertiary medical center. The exclusion criteria were baseline LVEF < 50%, the presence of heart disease possibly leading to impaired LVEF during follow-up, and prior chemotherapy. Clinical and echocardiographic follow-up were performed at baseline and every 3 months until treatment completion. The biplanar Simpson method was used to analyze LVEF, and mean regional GLS was obtained by 2-, 3-, and 4-chamber analyses. Additionally, hsTnI was measured during each treatment cycle and was considered positive when above the laboratory's reference threshold (> 40 ng/L). If CTRCD was present, then cardiac magnetic resonance imaging (cMRI) was also performed. Native T_1- and T_2-weighted values were obtained from the average value of the 16 short-axis segments in the T_1- and T_2-weighted mapping sequences. Extracellular volume was calculated based on the T_1-weighted mapping sequences before and after contrast administration. As per protocol, treatment was started with ACEIs or beta-blockers only in cases of moderate-to-severe CTRCD.

Table 1 lists the patients' baseline characteristics. Sequential treatment was given with anthracyclines and anti-HER2 therapy to 48.4% of patients, while anti-HER2 therapy without anthracyclines was given to the other 51.6%. During follow-up (mean, 13.6 months), symptomatic CTRCD did not appear in any patients. Nevertheless, the incidence of asymptomatic CTRCD was 60%: mild in 53 patients (55.8%), moderate in 3 (3.2%), and severe in 1 (1.1%). The mean time to CTRCD diagnosis was 162.1 days. In all, 3 patients experienced cancer progression, and 1 patient died from a noncardiovascular cause. In the bivariate analysis, cardiovascular risk factors and the use of dual anti-HER2 blockade with pertuzumab were not associated with the development of CTRCD. In the multivariate models adjusted for age, hypertension, dyslipidemia, diabetes, and use of pertuzumab, the only factor associated with CTRCD was the use of anthracyclines (odds ratio = 7.78; 95% confidence interval, 2.55-27.08; $P < .001$).

A total of 37 (38.9%) patients exhibited hsTnI elevation and 36 (37.9%) had > 15% change in GLS; 16 patients had both abnormalities. However, only 4 (4.2%) patients had moderate-to-severe CTRCD. Table 1 shows the distribution of the TnI, GLS, and LVEF abnormalities based on whether or not anthracyclines had been given. Table 2 lists the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of hsTnI and > 15% change in GLS in predicting the appearance of moderate-to-severe CTRCD. While the sensitivity, specificity, and PPV were poor for hsTnI and GLS, the NPV was 95.1% and 99%, respectively. In contrast, only 1 of 4 patients with moderate-to-severe CTRCD had hsTnI elevation, and although all also exhibited > 15% change in GLS, this change was not documented until moderate-to-severe CTRCD was diagnosed.

In keeping with the results of the Cardiotox registry,[3] our eHER2-bc cohort also showed a high incidence of mild CTRCD in the form of increased hsTnI and abnormal GLS, whereas the incidence of moderate-to-severe CTRCD was low (4.2%). As in other series,[4] the added value of hsTnI and GLS came mainly from their high NPV for predicting moderate-to-severe CTRCD,