REFERENCES

1. Jiménez-Méndez C, Díez-Villanueva P, Bonanad C, et al. Frailty and prognosis of older patients with chronic heart failure. *Rev Esp Cardiol.* 2022;75:1011–1019.
2. Kitzman DW, Whellan DJ, Duncan P, et al. Physical Rehabilitation for Older Patients Hospitalized for Heart Failure. *N Engl J Med.* 2021;385:203–216.
3. Pandey A, Segar MW, Singh S, et al. Frailty Status Modifies the Efficacy of Exercise Training Among Patients With Chronic Heart Failure and Reduced Ejection Fraction: An Analysis From the HF-ACTION Trial. *Circulation.* 2022;146:80–90.
4. The Vivifrail project. Available at https://www.vivifrail.com, Accessed 28 Apr 2023.
5. Martínez-Velilla N, Valenzuela PL, Sáez de Asteasu ML, et al. Effects of a Tailored Exercise Intervention in Acutely Hospitalized Oldest Old Diabetic Adults: An Ancillary Analysis. *J Clin Endocrinol Metab.* 2021;106:e899–e906.
6. Wielenga RP, Huisveld IA, Bol E, et al. Exercise training in elderly patients with chronic heart failure. *Coron Artery Dis.* 1998;9:765–770.

https://doi.org/10.1016/j.rec.2023.06.001

SGLT2i and loop diuretic withdrawal or downtitration in heart failure

iSGLT2 y retirada o reducción de diurético de asa en insuficiencia cardiaca

To the Editor,

Loop diuretics are the cornerstone of the treatment of fluid overload in heart failure (HF) but have possible deleterious effects on intravascular depletion and subsequent activation of the renin-angiotensin-aldosterone and sympathetic nervous systems. Sodium-glucose cotransporter 2 inhibitors (SGLT2i) reduce glucose and sodium resorption in the proximal tubule, causing natriuresis and osmotic diuresis due to glucosuria. Differences between the diuretic effects of SGLT2i vs loop diuretics suggest that SGLT2i may selectively reduce interstitial fluid, thereby avoiding deleterious reflex neurohumoral stimulation.[1] The effect of SGLT2i on the diuretic regimen in real-world ambulatory HF patients is not yet fully understood.

This study aimed to investigate diuretic use after the introduction of SGLT2i in outpatients with HF. As a secondary endpoint, lung ultrasound and HF biomarkers were assessed to monitor congestion status.

This prospective single-center study included ambulatory patients with nondecompensated HF and type-2 diabetes, irrespective of left ventricular ejection fraction (LVEF). The patients were receiving treatment with loop diuretics, and had an estimated glomerular filtration rate (eGFR) > 45 mL/min/1.73 m^{2*}. The study was performed in a HF clinic. All participant-sprovided written informed consent, and the protocol was approved by the local ethics committee (PI-18-163).

Study visits were performed at baseline and at 3 months of follow-up. At the initial visit, empagliflozin or dapagliflozin 10 mg/d were added to the HF treatment. As per the treatment protocol, clinicians were encouraged to reduce or withdraw diuretic treatment in accordance with their clinical assessment and were blinded to biomarker values. Neurohormonal HF medication could be adjusted, if clinically indicated.

Lung ultrasound was performed with a pocket device (V-scan, General Electric, United States) scanning 2 upper and 2 lower areas of each hemithorax, and images were analyzed offline.

The biomarker panel included N-terminal pro-B-type natriuretic peptide (NT-proBNP), cancer antigen 125 (CA125), and interleukin-1 receptor-like 1 (ST2).

The sums of B-lines and biomarker levels were compared between baseline and the 3-month follow-up.

From November 7, 2018 to March 25, 2021, 66 consecutive patients were included (mean age 67 years, predominantly male, with ischemic etiology, and mainly in New York Heart Association [NYHA] class II) (table 1). The mean LVEF was 43.7 ± 11.4 (30.2 ± 9.8 at admission to the HF clinic). The mean dose of furosemide or equivalent (10 mg torsemide = 40 mg furosemide) was 44.5 ± 29.6 mg/d.

After the introduction of SGLT2i, the number of patients treated with loop diuretics decreased by 50% ($P < .001$) (figure 1). Among the 33 patients who continued to receive loop diuretics, the mean dose was significantly reduced ($P < .001$) (figure 1); of note, these patients were receiving a higher dose of diuretics at baseline (61 ± 5 mg/d) than patients able to discontinue diuretic therapy (27.6 ± 11.1 mg/d), $P = .001$, and had a higher prevalence of chronic kidney disease and a history of previous HF hospitalization. The groups receiving empagliflozin (n = 29) vs dapagliflozin (n = 37) treatment did not differ in the percentage of patients with loop diuretic withdrawal ($P = .46$) or diuretic dose downtitration ($P = .63$). Only 1 patient returned to his previous dose of diuretic after withdrawal upon SGLT2i introduction.

There were no significant differences in the percentage of patients able to discontinue diuretic treatment based on etiology ($P = .08$). The percentage of these patients was higher in patients in NYHA functional class II (50%) than in those in NYHA III (28.5%), but this difference was not statistically significant, probably due to the small number of patients in class III ($P = .29$).

There were no significant changes in eGFR at 3 months of follow-up ($P = .20$) or in HF treatment at 3 months of follow-up. Indeed, only the percentage of angiotensin receptor-neprilysin inhibitors (ARNI) increased slightly from 48.9% to 53.4% ($P = .22$). Among treatment doses, only the ARNI dose increased statistically significantly from 233.3 ± 119.5 mg/d to 254.2 ± 114.3 mg/d, $P = .04$.

No significant changes were observed in the sum of B-lines ($P = .59$) or in biomarker concentrations (figure 1). There were no HF hospitalizations or deaths during follow-up.

Despite the limitation of the small sample size, our present results suggest that the introduction of SGLT2i treatment might facilitate withdrawal or dose-reduction of loop diuretics among ambulatory patients with HF, without evidence of worsening congestion, and assessed by either lung ultrasound or biomarkers of congestion.

In the pivotal clinical trials with SGLT2i in chronic HF, diuretic management was left to the investigators' discretion, and was rarely modified. In DAPA-HF,[2] the mean diuretic dose did not differ between groups after randomization, although a decrease in diuretic dose was more frequent with dapagliflozin. In EMPEROR-Reduced, patients in the empagliflozin group were less likely to require diuretic intensification.[3] Recently, a retrospective study of both empagliflozin and diuretics[4] showed that diuretics were reduced in 21% of patients and the mean dose of furosemide by about half.

In the current study, we evaluated additional information on fluid overload. Our results showed that SGL2i initiation and simultaneous dose reduction of loop diuretic did not significantly increase the number of B-lines or biomarker values.

Table 1
Demographic and clinical characteristics of the patients

Variable	Total N = 66	Diuretic Withdraw n = 33	No Diuretic Withdraw n = 33	P
Age	67.0 ± 9.8	65.8 ± 8.0	68.1 ± 11.4	.34
Male sex, n (%)	62 (93.9)	32 (97)	30 (90.9)	.30
Etiology				.08
Ischemic heart disease	32 (48.5)	15 (45.5)	17 (51.5)	
Dilated CM	21 (31.8)	14 (42.4)	7 (21.2)	
Hypertensive	5 (7.6)	2 (6.1)	3 (9.2)	
Valvular	4 (6.1)	0	4 (12.1)	
Other	4 (6.1)	2 (6.1)	2 (6.1)	
HF duration, years	6.3 ± 5.7	6.6 ± 6.1	6.0 ± 5.2	.66
Patients with HF hospitalization in previous year	16 (24.2)	6 (18.2)	10 (30.3)	.25
NYHA class, n (%)				.11
I	7 (10.6)	5 (15.2)	2 (6.1)	
II	52 (78.8)	26 (78.8)	26 (78.8)	
III	7 (10.6)	2 (6.1)	5 (15.2)	
LVEF, %	43.7 ± 11.4	45.1 ± 10.7	42.4 ± 12.2	.36
LVEF at the HF unit admission, %	30.2 ± 9.8	27.4 ± 8.5	32.9 ± 10.4	.02
HF therapy, n (%)				
ACEI or ARB	26 (39.4)	14 (42.4)	12 (36.4)	.61
ARNI	37 (56.1)	19 (57.6)	18 (54.5)	.80
Beta-blockers	64 (97.0)	33 (100)	31 (93.9)	.15
MRA	61 (92.4)	31 (93.9)	30 (90.9)	.64
Digoxin	16 (24.2)	7 (21.2)	9 (27.3)	.57
Ivabradine	20 (30.3)	10 (30.3)	10 (30.3)	1.00
CRT	12 (18.2)	6 (18.2)	6 (18.2)	1.00
ICD	18 (27.3)	11 (33.3)	7 (21.2)	.27
Dose of furosemide or equivalent (mg)	44.6 ± 29.6	27.6 ± 11.2	61.5 ± 32.6	< .001
Diuretic therapy, n (%)				
Furosemide	24 (27.3)	10 (30.3)	14 (42.4)	.31
Torsemide	42 (47.7)	23 (69.7)	19 (57.6)	.31
Thiazide	5 (7.6)	0	5 (15.2)	.02
Type 2 diabetes, years	9.7 ± 7.3	9.6 ± 6.6	9.6 ± 8.0	.99
Glycosylated hemoglobin	6.9 (6.5-7.8)	6.9 (6.5-7.4)	7.2 (6.4-8.0)	.48
Diabetes therapy, n (%)				
Metformin	57 (86.4)	28 (84.8)	29 (87.9)	.72
DPP4i	23 (34.8)	14 (42.4)	9 (27.3)	.20
Sulfonylurea	15 (22.7)	8 (24.2)	7 (21-2)	.77
Insulin	17 (25.8)	6 (18.2)	11 (33.3)	.16
Chronic kidney disease[a]*, n (%)*	9 (13.6)	2 (6.1)	7 (21.2)	.07
Haemoglobin, g/dL	13.8 ± 1.5	14.0 ± 1.5	13.7 ± 1.7	.40
eGFR (mL/min per 1.73m²)	66.2 ± 17.3	67.7 ± 17.2	65.2 ± 17.6	.56

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CA125, cancer antigen 125; CM, cardiomyopathy; CRT, cardiac resynchronization therapy; DPP4i: dipeptidyl dipeptidase-4 inhibitors; eGFR, estimated glomerular filtration rate; GLP1RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; ICD, implantable cardiac defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; sST2, soluble interleukin-1 receptor-like 1.

[a] Estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration equation) < 60 mL/min per 1.73 m^2.

Data in mean ± standard deviation, median [Q1-Q3], or n (%).

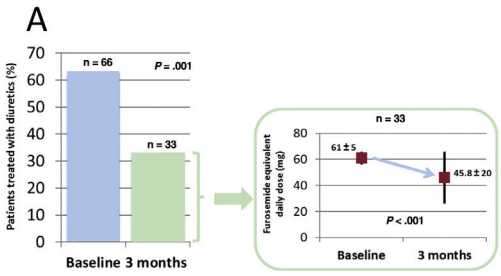
Because this was a nonrandomized single-center study with stable patients treated at a specialized HF clinic, we cannot exclude the possibility that the patients might have tolerated diuretic downtitration even without the introduction of SGLT2i. Nevertheless, our data indicate that loop diuretic withdrawal or downtitration with SGLT2i introduction was safe in low-risk outpatients and did not worsen congestion across the spectrum of HF, as suggested in previous publications.[5]

FUNDING

None.

AUTHORS' CONTRIBUTIONS

M. Domingo, J. Lupón, N. Alonso Pedrol and A. Bayés-Genís conceived and designed the study; M. Domingo Teixidor and J.



B

	Baseline	3 months	*P*-value
B-lines sum, n	3 [1-4.25]	2 [0-4]	0.59
NT-proBNP ng/L	472 [204-894]	496 [174-1078]	0.07
CA125 U/mL	13.1 [9.1-17.1]	13.0 [9.6-17.2]	0.58
ST2 ng/L	30.2 [20.6-40.4]	34.3 [22.8-37.8]	0.75

Figure 1. Sodium-glucose cotransporter 2 inhibitors and diuretic withdrawal or downtitration effect. A: SGLT2i diuretic withdrawal or dose reduction in patients who remained on diuretic treatment. B: lung congestion and biomarkers at baseline and follow-up. NT-proBNP, N-terminal pro-B-type natriuretic peptide; CA125, cancer antigen-125; ST2, interleukin-1 receptor-like 1.
Data are expressed as median [interquartile range].

Lupón wrote the study; M. Domingo Teixidor, M. Ruiz-Cueto, A. Teis Soley and N. Alonso Pedrol acquired the data; J. Lupón performed the statistical analysis.

CONFLICTS OF INTEREST

A. Bayés-Genís reports honoraria from AstraZeneca and Boehringer-Ingelheim. The remaining authors declare no conflict of interest.

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Available online 16 June 2023

REFERENCES

1. Hallow KM, Helmlinger G, Greasley PJ, et al. Why do SGLT2 inhibitors reduce heart failure hospitalization?. A differential volume regulation hypothesis. *Diabetes Obes Metab.* 2018;20:479–487.
2. Jackson AM, Dewan P, Anand IS, et al. Dapagliflozin and Diuretic Use in Patients With Heart Failure and Reduced Ejection Fraction in DAPA-HF. *Circulation.* 2020;142:1040–1054.
3. Packer M, Anker SD, Butler J, et al. Empagliflozin in PatientsWith Heart Failure, Reduced Ejection Fraction, and Volume Overload: EMPEROR-Reduced Trial. *J Am Coll Cardiol.* 2021;77:1381–1392.
4. Kim SJ, Kim BJ, Im SI, et al. Effects of Empagliflozin on Diuretics Reduction in Outpatient Heart Failure Patients. *Int J Heart Fail.* 2022;4:183–192.
5. Requena-Ibáñez JA, Santos-Gallego CG, Badimón JJ. SGLT2i in heart failure: can their benefits be expanded across the entire spectrum of ejection fraction? *Rev Esp Cardiol.* 2022;75:833–841.

https://doi.org/10.1016/j.rec.2023.06.002