The 3 cases described in this report show that a previous diagnosis of cardiomyopathy does not rule out CA. All 3 patients had clinical and echocardiographic red flags for CA while under follow-up for HCM or titin cardiomyopathy. Cardiologists should always be alert to possible red flags for CA in patients older than 65 or 70 years, especially in the presence of left ventricular hypertrophy or worsening symptoms.[4–6] An existing diagnosis of cardiomyopathy should not preclude tests for CA, as both conditions can clearly coexist.

FUNDING

No funding was received for this study.

ETHICAL CONSIDERATIONS

Approval from the local ethics committee was not needed due to the characteristics of the study. The authors confirm that they received written informed consent from the patients for the publication of the text and images included in this article. Sex and gender were reported in accordance with the Spanish Sex and Gender Equity in Research (SAGER) guidelines.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

No artificial intelligence tools were used for this study.

AUTHORS' CONTRIBUTIONS

E. Martín-Álvarez, R. Barriales-Villa, and J.M. Larrañaga-Moreira designed the study, prepared the figures, and wrote the manuscript. G. Barge-Caballero, M.G. Crespo-Leiro, and B. Souto-Caínzos critically reviewed the manuscript.

CONFLICTS OF INTEREST

J. M. Larrañaga Moreira, M. G. Crespo Leiro, and R. Barriales Villa report have received funding from Pfizer for attending conferences.

M. G. Crespo Leiro received funding from Pfizer at her institute for participating in a clinical trial.

R. Barriales Villa has performed consultancy work for Pfizer, Alnylam, and Akcea.

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https://doi.org/10.1016/j.recesp.2023.09.012

Use of SGLT2i in patients with transthyretin amyloid cardiomyopathy: prevalence and safety in a Spanish prospective cohort

Uso de iSGLT2 en pacientes con amiloidosis cardiaca por transtirretina: prevalencia y seguridad en una cohorte prospectiva en España

To the Editor,

Few data are available on the usefulness of drugs typically used to treat heart failure (HF) in patients with transthyretin cardiac amyloidosis (ATTR-CA). Of these medications, the most pertinent drug class is possibly sodium-glucose cotransporter type 2 inhibitors (SGLT2i) because they are indicated for both heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF).[1] The latter is the form with the most frequent clinical presentation in ATTR-CA patients.[2] The proven diagnostic benefit of this class of medications in all ejection fraction types, as well as its diuretic effect and favorable hemodynamic profile, suggests that it could be a good therapeutic option in patients with ATTR-CA. However, because this population is systematically excluded from clinical trials of SGLT2i, its effectiveness and safety profile in ATTR-CA are unknown. Accordingly, we examined the prevalence of SGLT2i use and the safety of the drugs in a cohort of patients with ATTR-CA.

We established a prospective registry of all patients diagnosed with ATTR-CA in our center between January 1, 2018, and July 31, 2022, and identified all patients who received any treatment with an SGLT2i. All adverse events potentially associated with this drug class were recorded via a retrospective review of electronic medical records from the date of treatment initiation to discontinuation, patient death, or end of the observation period, established at November 30, 2022. Participant follow-up was conducted in the Heart Failure Unit at least every six months. All

Table 1
Patients' baseline characteristics at the time of registry inclusion

Characteristics	ATTR-CA with SGLT2i (n = 64)	ATTR-CA without SGLT2i (n = 112)	*P*
Demographic			
Age, y	80.8 [77.5-83.4]	83.0 [79.2-86.6]	.085
Female sex	11 (17.2)	33 (29.5)	.074
Nonhereditary ATTR-CA	63 (98.4)	98 (87.5)	.043
Hereditary ATTR-CA[a]	0	2 (1.8)	
ATTR-CA without a genetic study	1 (1.6)	12 (10.7)	
Clinical history			
Hypertension	39 (60.9)	83 (74.1)	.089
Hypercholesterolemia	41 (64.1)	66 (58.9)	.525
Smoking	17 (26.6)	32 (28.6)	.862
Diabetes mellitus	25 (39.1)	21 (18.8)	.004
Fibrillation or atrial flutter	37 (57.8)	51 (45.5)	.158
Hospitalization for HF	25 (39.1)	31 (27.7)	.132
Ischemic heart disease	13 (20.3)	13 (11.6)	.127
Stroke	10 (15.6)	14 (12.5)	.649
Peripheral artery disease	5 (7.8)	6 (5.4)	.531
Bilateral carpal tunnel syndrome	20 (31.3)	23 (20.5)	.144
Clinical presentation			
Systolic blood pressure, mmHg	123 [113-135]	127 [114-138]	.286
Diastolic blood pressure, mmHg	76 [66-81]	75 [65-82]	.549
Heart rate, bpm	72 [61-82]	75 [60-86]	.143
NYHA III or IV	18 (28.1)	32 (28.6)	.999
Signs of congestion[b]	34 (53.1)	59 (52.7)	.999
Laboratory data			
NT-proBNP, pg/mL	2450 [1080-5929]	2280 [1007-4503]	.522
Hemoglobin, g/dL	13.9 [12.6-15.1]	13.4 [12.1-14.8]	.103
Creatinine, mg/dL	1.1 [1.0-1.4]	1.1 [0.9-1.3]	.485
Urea, mg/dL	66.5 [55.0-83.5]	60.0 [48.2-84.7]	.066
eGFR, mL/min	51.1 [43.7-61.7]	52.2 [40.1-65.4]	.999
Potassium, mEq/L	4.4 [4.2-4.8]	4.4 [4.1-4.8]	.945
Sodium, mEq/L	141 [139-143]	141 [139-142]	.278
Bilirubin, mg/dL	0.9 [0.6-1.3]	0.8 [0.6-1.0]	.193
Uric acid, mg/dL	7.1 [5.9-8.1]	6.9 [5.4-8.6]	.638
Glucose, mg/dL	104 [91-116]	98 [88-108]	.051
Glycated hemoglobin, %	6.1 [5.6-6.5]	5.8 [5.5-6.2]	.107
Echocardiogram			
LVEF, %	49 [40.9-57.8]	55.5 [47.5-63.8]	.010
TAPSE, mm	16 [13-18]	17 [14-20]	.002
Medical therapy			
Antiplatelet agents	12 (18.8)	14 (12.5)	.276
Anticoagulants	38 (59.4)	53 (47.3)	.158
Loop diuretics	47 (73.4)	80 (71.4)	.862
Thiazide diuretics	5 (7.8)	19 (17.0)	.111
Beta-blockers	33 (51.6)	44 (39.3)	.118
ACEIs/ARBs/VS	31 (48.4)	53 (47.3)	.995
MRAs	21 (32.8)	26 (23.2)	.215
Lipid-lowering agents	41 (64.1)	66 (58.9)	.525
Non-SGLT2i antidiabetic agents	23 (35.9)	21 (18.8)	.018

ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; ATTR-CA, transthyretin cardiac amyloidosis; eGFR, estimated glomerular filtration rate by the Cockcroft-Gault equation; HF, heart failure; LVEF, left ventricular ejection fraction; MRAs, mineralocorticoid receptor antagonists; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SGLT2i, sodium-glucose cotransporter-2 inhibitor; TAPSE, tricuspid annular plane systolic excursion; VS, valsartan/sacubitril.
Categorical variables are presented as No. (%) and continuous variables as median [interquartile range].
[a] Both cases of hereditary ATTR-CA had the p.Val50Met variant.
[b] As a variable, signs of congestion was defined by a physical examination finding of jugular venous distension, lower limb edema, or coarse crackles in the pulmonary fields.

Table 2
Detailed description of the adverse events observed in the cohort

Patient	Sex	Age, y	Drug	Indication	AE	Days to AE	Reason for treatment end	Days on treatment
1	Male	85	Empagliflozin 25 mg	Diabetes	UTI due to *Enterococcus faecalis*	408	Death (ischemic heart disease)	413
2	Male	83	Dapagliflozin 10 mg	HFrEF	Balanitis	506	End of follow-up	520
3	Female	78	Dapagliflozin 10 mg	HFrEF	UTI due to *Streptococcus agalactiae* and *Proteus mirabilis*	206	End of follow-up	307
4	Male	61	Empagliflozin 10 mg	HFpEF	3 UTIs due to *Escherichia coli*	36	Repeated UTI	95

AE, adverse event; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; UTI, urinary tract infection.

patients signed an informed consent form before their inclusion in the registry.

Of a total of 176 patients with ATTR-CA, 64 (36.4%) had received a treatment with an SGLT2i (47 [73.4%] with empagliflozin, 16 [25%] with dapagliflozin, and 1 [1.6%] with canagliflozin). Of these, 13 were already receiving the drug at the time of their inclusion in the registry and 51 were prescribed it later. The median time to drug initiation was 940 [interquartile range, 377-1176] days. The most common indication was HFpEF (28 patients, 43.8%), followed by HFrEF (19 patients, 29.7%) and diabetes mellitus type 2 (17 patients, 26.6%).

The median patient age was 80.8 years and there were 11 women (17.2%). At the time of registry inclusion, most patients (46 [71.9%]) were in New York Heart Association class I or II, 34 (53.1%) had signs or symptoms of congestion, and 25 (39.1%) had already been hospitalized at least once for HF. The most frequently prescribed drug class was loop diuretics (47 patients, 73.4%), while neurohormonal modulators were used in less than half of the cohort. The baseline characteristics of the population are shown in table 1.

During a median SGLT2i treatment time of 304 [76-482] days, 3 patients (4.7%) had a urinary infection and 1 (1.6%) had a genital infection (table 2). This drug class was not associated with fracture, ketoacidosis, hypoglycemia, hypotension, amputation, or Fournier gangrene. In addition, 2 patients (3.1%) discontinued the SGLT2i therapy, 1 due to repeat urinary infections (Case No. 4 of table 2) and the other (a 64-year-old man taking empagliflozin 10 mg for HFpEF) of his own accord and without clinical justification.

The median follow-up of the cohort from inclusion in the registry was 790 [401-1245] days and 45 deaths occurred in total (25.6%) (6 in the SGLT2i group [9.4%] and 39 in the non-SGLT2i group [34.8%]).

In summary, our single-center and prospective cohort of patients with ATTR-CA revealed that slightly more than a third of participants were treated with an SGLT2i and that these drugs are safe and well-tolerated. The only adverse events observed were urinary and genital infections and only 1 patient discontinued the treatment. A review of the literature revealed just 2 studies that also included patients with ATTR-CA treated with SGLT2is. In the first,[3] 15 patients with this heart condition and diabetes mellitus received a member of this drug class (dapagliflozin in 53%) during a median of 8 months. No urinary or genital infections were detected and the treatment was discontinued in 2 patients due to the development of constipation and HF deterioration, respectively. In the second study,[4] clinical course and biomarkers were compared between 17 patients with ATTR-CA treated with dapagliflozin and 40 patients with ATTR-CA who were not treated with dapagliflozin. The authors did not detect any adverse events associated with the drug during a median treatment duration of 3 months.

The main limitations of the current study are the small sample size and its single-center design, which limits the extrapolation of the results to other populations. The main strength of the study is that, to date, it includes the largest series of patients with ATTR-CA treated with an SGLT2i and that the results indicate that these drugs are safe and well-tolerated in this population. Observational studies with a larger sample size and longer follow-up duration are required, as well as clinical trials, to verify our hypothesis and assess the effects of these drugs on cardiovascular morbidity and mortality.

FUNDING

The authors did not receive specific funding for the preparation of this manuscript.

ETHICAL CONSIDERATIONS

The authors of this article accept full responsibility for its content as defined by the International Committee of Medical Journal Editors. The included patients signed an informed consent form before their participation. Possible sex and gender biases have been considered.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

Artificial intelligence was not used.

AUTHORS' CONTRIBUTIONS

All authors have contributed equally to the drafting of this document.

CONFLICTS OF INTEREST

The authors do not declare conflicts of interests in relation to this work.

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