Rev Esp Cardiol. 2024;77(6):481–489

Original article

Impact of initiation of SGLT2 inhibitor treatment on the development of arrhythmias in patients with implantable cardiac devices

Carlos Minguito-Carazo,[a,*] Enrique Sánchez Muñoz,[b] Moisés Rodríguez Mañero,[a,c,d] José Luis Martínez-Sande,[a] María Luisa Fidalgo Andrés,[b] Javier García Seara,[a] José María González Rebollo,[b] Miguel Rodríguez Santamarta,[b] Laila González Melchor,[a] Teba González Ferrero,[a] Laura Romero Roche,[b] Jesús Alberto Fernández López,[a] Elena Tundidor Sanz,[b] Felipe Fernández Vázquez,[b] and José Ramón González-Juanatey[a,c,d]

[a] *Servicio de Cardiología, Hospital Universitario de Santiago de Compostela (CHUS), Santiago de Compostela, A Coruña, Spain*
[b] *Servicio de Cardiología, Complejo Asistencial Universitario de León, León, Spain*
[c] *Grupo de Cardiología Traslacional, Instituto de Investigación Sanitaria de Santiago de Compostela (IDIS), Santiago de Compostela, A Coruña, Spain*
[d] *Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Spain*

Article history:
Received 3 August 2023
Accepted 11 December 2023
Available online 19 January 2024

Keywords:
Sodium glucose transporter 2 (SGLT2)
Implantable cardiac device
Cardiac arrhythmia

ABSTRACT

Introduction and objectives: Sodium-glucose cotransporter type 2 inhibitors (SGLT2i) have been associated with improved prognosis in patients with heart failure, but their impact on atrial arrhythmic (AA) and ventricular arrhythmic (VA) events is not fully understood.
Methods: This multicenter retrospective study included patients with implantable cardioverter-defibrillators who initiated treatment with SGLT2i. AA and VA events were compared in 2 time periods for each patient: 1 year before and 1 year after starting SGLT2i.
Results: The study included 195 patients (66.8 [61.3-73.1] years, 18.5% women). In the post-SGLT2i period, there was a reduction in the percentage of patients with any VA (pre: 52.3% vs post: 30.3%; $P < .001$) and clinically relevant VA (excluding nonsustained ventricular tachycardia) (pre: 21.5% vs post: 8.7%; $P < .001$). There was also a decrease in the number of episodes per patient/y of nonsustained ventricular tachycardia (pre: 2 (1-5) vs post: 1 (0-2); $P < .001$) and sustained ventricular tachycardia (pre: 1 (1-3) vs post: 0 (0-2); $P = 0.046$). However, no differences were observed in the prevalence of AA (24.7% vs 18.8%; $P = .117$) or the burden of atrial fibrillation (pre: 0% (0-0.1) vs post: 0% (0-0); $P = .097$).
Conclusions: Initiation of SGLT2i treatment was associated with a decrease in the percentage of patients with relevant VA but this effect was not observed for AA.
© 2023 Sociedad Española de Cardiología. Published by Elsevier España, S.L.U. All rights reserved.

Impacto del inicio del tratamiento con iSGLT2 en el desarrollo de arritmias en pacientes portadores de dispositivos cardiacos implantables

Palabras clave:
Cotransportador de sodio-glucosa tipo 2 (SGLT2)
Dispositivo cardiaco implantable
Arritmias cardiacas

RESUMEN

Introducción y objetivos: Los inhibidores del cotransportador de sodio-glucosa tipo 2 (iSGLT2) se han asociado con una mejoría pronóstica en pacientes con insuficiencia cardiaca. Sin embargo, su impacto en las arritmias auriculares (AA) y ventriculares (AV) no se conoce del todo.
Métodos: Estudio retrospectivo multicéntrico que incluyó a pacientes portadores de desfibrilador automático implantable que iniciaron tratamiento con iSGLT2. Se compararon las AA y AV en 2 periodos de tiempo para cada paciente: 1 año antes y 1 año después de iniciar el iSGLT2.
Resultados: Se incluyó a 195 pacientes (media de edad, 66,8 [61,3-73,1] años; el 18,5% mujeres). Se registró una reducción en el porcentaje de pacientes con cualquier AV (antes frente a después, el 52,3 frente al 30,3%; $p < 0,001$) y con AV clínicamente relevantes (excluida la taquicardia ventricular no sostenida) (el 21,5 frente al 8,7%; $p < 0,001$) en el periodo post-iSGLT2. Se observó también una reducción en la incidencia del número de episodios de taquicardia ventricular no sostenida por paciente/año —antes frente a después, 2 (1-5) frente a 1 (0-2) ($p < 0,001$)— y de taquicardia ventricular sostenida —1 (1-3) frente a 0 (0-2) ($p = 0,046$)—. No se observaron diferencias en la prevalencia de AA (el 24,7 frente al 18,8%; $p = 0,117$) ni en la carga de fibrilación auricular: el 0 (0-0,1) frente al 0 (0-0) ($p = 0,097$).

* Corresponding author.
E-mail address: carlosminguito@hotmail.es (C. Minguito-Carazo).
@CarlosMinguito

https://doi.org/10.1016/j.rec.2023.12.010
1885-5857/© 2023 Sociedad Española de Cardiología. Published by Elsevier España, S.L.U. All rights reserved.

Conclusiones: Tras el inicio del tratamiento con iSGLT2, se observó una reducción del porcentaje de pacientes con AV relevantes. Este efecto no se registró en las AA.
© 2023 Sociedad Española de Cardiología. Publicado por Elsevier España, S.L.U. Todos los derechos reservados.

Abbreviations

AA: atrial arrhythmia
ICD: implantable cardioverter-defibrillator
SGLT2i: sodium-glucose cotransporter 2 inhibitor
SVT: sustained ventricular tachycardia
VA: ventricular arrhythmia

INTRODUCTION

In recent years, sodium-glucose cotransporter 2 inhibitors (SGLT2is) have demonstrated prognostic improvements in various studies of patients with heart failure.[1–4] These drugs are 1 of the 4 pillars of the recommended medical therapy in current clinical practice guidelines, together with beta-blockers, mineralocorticoid receptor antagonists (MRAs), and angiotensin receptor/neprilysin inhibitors (ARNIs).[5,6]

Several studies have linked the use of these drugs to reductions in sudden cardiac death (SCD) and in the incidences of atrial arrhythmia (AA) and atrial fibrillation (AF).[7,8] However, their impact on arrhythmic events is incompletely understood and some studies have reached contradictory conclusions.[9,10] This might be because only clinically symptomatic events are reported and not arrhythmic episodes that are asymptomatic but have prognostic value. Such episodes can only be detected in patients with continuous electrocardiographic monitoring. Thus far, just 1 observational study has assessed the association of SGLT2i treatment with reductions in AA and ventricular arrhythmia (VA) in patients with cardiac implantable electronic devices (CIEDs)[11]; the results indicated a reduction in AAs but not in VAs. Nonetheless, the study groups were not completely comparable because the patients receiving SGLT2i were younger and were more likely to have an implantable cardioverter-defibrillator (ICD) or cardiac resynchronization therapy (CRT) device. Accordingly, the objective of the current study was to assess the impact of SGLT2i initiation on the prevalence and incidence of AA and VA in a cohort of patients with an ICD by comparing events in 2 similar periods before and after drug initiation.

METHODS

Population

The present retrospective multicenter study was conducted in 2 centers and included patients with an ICD with or without associated CRT who started treatment with an SGLT2i between January 2015 and January 2022. The study inclusion criteria were as follows: *a)* indication for treatment with SGLT2i (heart failure [HF] or diabetes mellitus); *b)* implanted with an ICD/CRT-ICD at least 1 year before SGLT2i initiation; and *c)* complete follow-up for at least 1 year after treatment initiation. The variable HF was defined as the presence of hospitalization for HF or an ambulatory New York Heart Association (NHYA) functional class > I under follow-up in the HF unit in each center. Follow-up was divided into 2 periods of equal length: the first period was 1 year prior to SGLT2i initiation (pre-SGLT2i) while the second period was 1 year after drug initiation (post-SGLT2i). Arrhythmic events were compared between the 2 periods. The study was approved by the local ethics committee of each center and all surviving patients at the time of analysis provided signed informed consent authorizing their participation.

Collection of arrhythmic events

Events were recorded in face-to-face consultations or via remote monitoring. All recorded episodes were analyzed by 2 electrophysiologists specialized in the reading of intracavitary tracings. If there were doubts about the type of event, the 2 electrophysiologists analyzed them together to reach a final diagnosis. For patients with remote monitoring, episodes occurring during the 2 periods were recorded using the different available platforms. For the remainder, episodes were collected from medical records. A nonsustained ventricular tachycardia (NSVT) event was defined as the presence of 3 or more ventricular complexes while sustained ventricular tachycardia (SVT) was defined as a ventricular tachycardia > 30 seconds or requiring device therapy for resolution. A ventricular fibrillation (VF) event was defined as any ventricular tachyarrhythmia with a heart rate > 200 bpm. If the episode was still not resolved after an appropriate therapy, it was counted within the same episode. An appropriate therapy was defined as the presence of anti-tachycardia pacing (ATP) episodes or appropriate ICD discharge. We calculated the incidences of NSVT, SVT, ATP, VF, and appropriate and inappropriate ICD discharges, as well as the number of episodes per patient/y. VAs with a lower heart rate than the first programmed tachycardia window in the device were not recorded or included in the analysis.

For AAs, we collected atrial high-rate episodes and AF episodes of 30 seconds to 6 minutes, 6 minutes to 24 hours, and > 24 hours. The variable any AA was defined as the presence of any episode, regardless of duration. Information was obtained on AF burden from patients with devices providing these data. To compare AA events between the 2 periods, patients with permanent AF were excluded.

Endpoints

The main endpoint of the study was assessment of the differences in the percentages of patients with relevant VAs (RVAs) and with any type of VA in the 2 periods. RVA was defined as any episode of SVT, VF, ATP, or appropriate ICD discharge. The variable any type of VA was defined as the presence of RVA or NSVT. The secondary study endpoints included the differences between the percentages of patients with NSVT, SVT, VF, ATP, or appropriate discharge and in the incidences of episodes per patient between the 2 periods.

Another end point related to AA events was defined as the difference in the percentage of patients with any AA episodes, as well as their duration. We also assessed differences in their incidence and in AF burden.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation or median [interquartile range] according to normality, which was determined using the Shapiro-Wilk test. Categorical variables are expressed as number and percentage and were compared using the chi-square test or Fisher exact test. Continuous variables were compared using the *t* test or Wilcoxon matched-pair test while categorical variables before and after SGLT2i initiation were compared using the McNemar test. A sensitivity analysis was performed by excluding patients with events in the first 30 days after SGLT2i initiation, to allow a certain amount of time to pass before the drug took effect. To evaluate the influence of SGLT2i use on the reduction in arrhythmic events, we constructed a multivariable regression model using the generalized estimating equation method by including as confounding variables the various concomitant treatments in each period (angiotensin-converting enzyme inhibitors [ACEIs] or angiotensin II receptor blockers [ARBs], ARNIs, beta-blockers, MRAs, amiodarone, and any antiarrhythmic agent). $P < .05$ was considered statistically significant. STATA version 15.1 was used for all analyses (STATA Corp, United States).

RESULTS

Population

Of the 442 patients with an ICD and under treatment with an SGLT2i, we excluded 247 due to an insufficient follow-up before or after the treatment. Ultimately, 195 patients were included (18.5% women; mean age, 66.8 [61.3 ± 73.1] years); 43.5% of the entire cohort had a diagnosis of AF before inclusion. Most (89.7%) had a clinical diagnosis of HF and the most prevalent etiology was ischemic (63%).

In addition, 132 of the patients (67.7%) had an ICD; the remainder had a CRT-ICD. Overall, 68.2% had a single-chamber device; of the CRT-ICD patients, 74.6% had an atrial lead. The implantation indication was primary prevention in 77.9% of cases. For 157 patients (80.5%), follow-up was conducted using remote monitoring in both periods; outpatient follow-up was performed for the remainder. Regarding the programming, 100% of the patients had a VF zone (212 ± 9.6 bpm), 95.4% had a rapid ventricular tachycardia (VT) zone (176 ± 7.6 bpm), and 5.6% had a slow VT zone (158 ± 30.3 bpm) (table 1).

The treatment indication was HF in 175 patients (89.7%) and diabetes mellitus in the remainder; the most commonly used SGLT2i was dapagliflozin (71.8%). A higher percentage of patients were under treatment with an ACEI/ARB (28.4% vs 16.8%, $P < .001$) in the first period vs the second while a lower percentage of patients were being treated with ARNIs (73.3% vs 83.6%, $P < .001$). There were no differences between the 2 periods in the percentage of patients under treatment with MRAs, beta-blockers, amiodarone, antiarrhythmic agents for HF, sotalol, or digoxin or in the percentage of treatment time with each drug (table 2).

During follow-up, 2 patients (1.0%) underwent pulmonary vein isolation and 16 (8.2%) underwent VT ablation. AF was diagnosed in 12 patients (6.8%), 16 (8.2%) were admitted for arrhythmia, and 24 (12.3%) for decompensated HF. After a mean follow-up period of 30.8 (26.7-37.0) months, 8 patients (4.1%) died during the study period.

Ventricular arrhythmias

Of the complete cohort, 102 patients (52.3%) exhibited some type of VA in the period prior to SGLT2i initiation vs 59 (30.3%) after treatment initiation ($P < .001$). Of the patients who experienced a RVA, 42 (21.5%) had an episode in the first period vs 17 (8.7%) in the second ($P < .001$) (figure 1). This decrease in VA was due to a fall in the percentage of patients with NSVT (44.1% vs 27.2%, $P < .001$), SVT (17.4% vs 7.2%, $P < .001$), and APT (12.8% vs 6.7%, $P = .023$). Although decreases were detected in the number of patients with VF (5.2% vs 1.5%, $P = .052$) and with appropriate ICD discharge (6.7% vs 3.1%, $P = .07$), the differences were not significant. The number of patients with appropriate ICD therapy fell in the post-SGLT2i period (14.9% vs 7.7%, $P = .011$) (figure 2 and table 3). In addition, on multivariate analysis, the protective effect of the SGLT2is was maintained for both all types of VA (odds ratio [OR] = 0.35; 95% confidence interval [95%CI], 0.24-0.5; $P < .001$) and for RVAs (OR = 0.30; 95%CI, 0.17-0.52; $P < .001$).

In sensitivity analysis, after excluding patients with events within 30 days after drug initiation, we observed similar results for both any type of VA (41.9% vs 15.0%, $P < .001$) and RVAs (21,7% vs 8.3%, $P < .001$). These results were recorded both in patients with an ICD indication for primary prevention (any VA, 52.0% vs 28.9%,

Table 1
Baseline characteristics of the cohort

Variable	Population (n = 195)
Age, y	66.8 [61.3-73.1]
Women	36 (18.5)
Hypertension	123 (63.1)
Dyslipidemia	121 (62.1)
Diabetes mellitus	54 (27.7)
COPD	14 (7.2)
CKD	21 (10.8)
Atrial fibrillation	85 (43.5)
Paroxysmal atrial fibrillation	42 (21.5)
Persistent atrial fibrillation	2 (1.0)
Permanent atrial fibrillation	41 (21.0)
Clinical heart failure	175 (89.7)
Type of heart disease	
Ischemic	109 (63.0)
Nonischemic dilated	59 (29.5)
Valvular heart disease	6 (3.5)
Infiltrative	0 (0)
Cardiomyopathy	3 (1.7)
Toxic	3 (1.7)
Tachycardiomyopathy	1 (0.6)
HF duration, mo	53.0 [30.3-113.2]
LVEF, %	30 [25-36]
Type of LVEF	
LVEF > 50%	11 (5.6)
LVEF 40%-50%	17 (8.7)
LVEF < 40%	167 (85.6)
Device type	
ICD	132 (67.7)
CRT-ICD	63 (32.3)
Time from device implantation, mo	19.4 [8.2-38.8]
Primary prevention	152 (77.9)
Secondary prevention	43 (22.1)

CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction.
Data are expressed as No. (%) or median [interquartile range].

Table 2
Drug therapy received in the 2 periods

Drug	Pre-SGLT2i	Post-SGLT2i	*P*
ACEIs/ARBs	56 (28.4)	33 (16.8)	< .01
Time on ACEIs/ARBs, %	99.9 [99.9-99.9]	99.9 [99.9-99.9]	.103
ARNIs	143 (73.3)	163 (83.6)	< .01
Time on ARNIs, %	99.9 [99.9-99.9]	99.9 [99.9-99.9]	.642
MRAs	177 (90.8)	179 (91.8)	.317
Time on MRAs, %	99.9 [99.9-99.9]	99.9 [99.9-99.9]	.171
Beta-blockers	193 (98.8)	192 (98.5)	.317
Time on beta-blockers, %	99.9 (99.9-99.9)	99.9 [99.9-99.9]	.05
Amiodarone	33 (16.9)	35 (18.1)	.593
Time on amiodarone, %	99.9 [99.9-99.9]	99.9 [99.9-99.9]	.290
Class Ic antiarrhythmic agents	0	0	>.999
Sotalol	1 (0.5)	3 (1.54)	.157
Digoxin	17 (8.7)	16 (8.2)	.655

ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; ARNIs, angiotensin receptor-neprilysin inhibitors; MRAs, mineralocorticoid receptor antagonists; SGLT2i, sodium-glucose cotransporter-2 inhibitor.
Data are expressed as No. (%) or median [interquartile range].

P < .001; RVA, 19.7% vs 6.6%, *P* < .001) and secondary prevention (any VA, 54.7% vs 35.7%, *P* = .033; RVA, 31.0% vs 16.8%, *P* = .034), as well as after the exclusion of patients who underwent VT ablation (VA, 51.4% vs 29.1%, *P* < .001; RVA, 19.0% vs 6.2%, *P* < .001). Given the higher number of patients with ARNIs in the post-SGLT2i period, we performed a subanalysis excluding patients who began treatment with this drug in the second period. Similar results were obtained (VA, 52.6% vs 31.4%, *P* < .001; RVAs, 20.6% vs 9.1%, *P* < .001).

Regarding the incidence of VA, the number of NSVT episodes per patient/y decreased in the post-SGLT2i period (before vs after, 2 [1-5] vs 1 [0-2], *P* < .001), as well as those of SVT (1 [1-3] vs 0 [0-2], *P* = .046) and ATP (1 [0-3] vs 0 [0-2], *P* = .045). There was no significant reduction in the incidence of VF episodes (1 [1-1] vs 0 [0-0], *P* = .054) or in the number of episodes with appropriate (1 [0-2] vs 0 [0-1], *P* = .399) and inappropriate (1 [0.5-1] vs 0 [0-0.5], *P* = .179) ICD discharges.

Atrial arrhythmias

Of the 85 patients (43.5%) with AF prior to study inclusion, 42 (49.4%) had paroxysmal AF, 2 (2.4%) had persistent AF, and 41 (48.2%) had permanent AF. Excluding the latter group, no decrease was recorded in the percentage of patients with AA events lasting from 6 minutes to 24 hours (13.0% vs 10.4%, *P* = .371) or those lasting more than 24 hours (6.5% vs 7.9%, *P* = .617). However, there was a reduction in the percentage of patients with episodes lasting from 30 seconds to 6 minutes (14.9% vs 7.8%, *P* = .034). Among the patients who had some type of AA, there were also no differences in the incidences of AA episodes lasting from 30 seconds to 6 minutes (*P* = .143), from 6 minutes to 24 hours (*P* = .309), or for more than 24 hours (*P* = .843). In addition, despite a fall in the percentage of patients with any AA, the difference was not statistically significant (24.7% vs 18.8%, *P* = 117) (figure 3). These results were maintained when

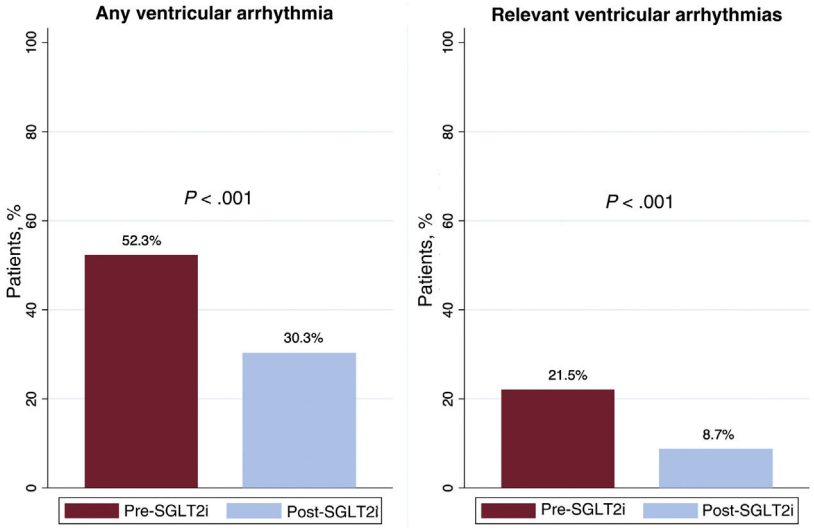

Figure 1. Percentages of patients with any ventricular arrhythmia and with relevant ventricular arrhythmias in the 2 periods. SGLT2i, sodium-glucose cotransporter 2 inhibitor.

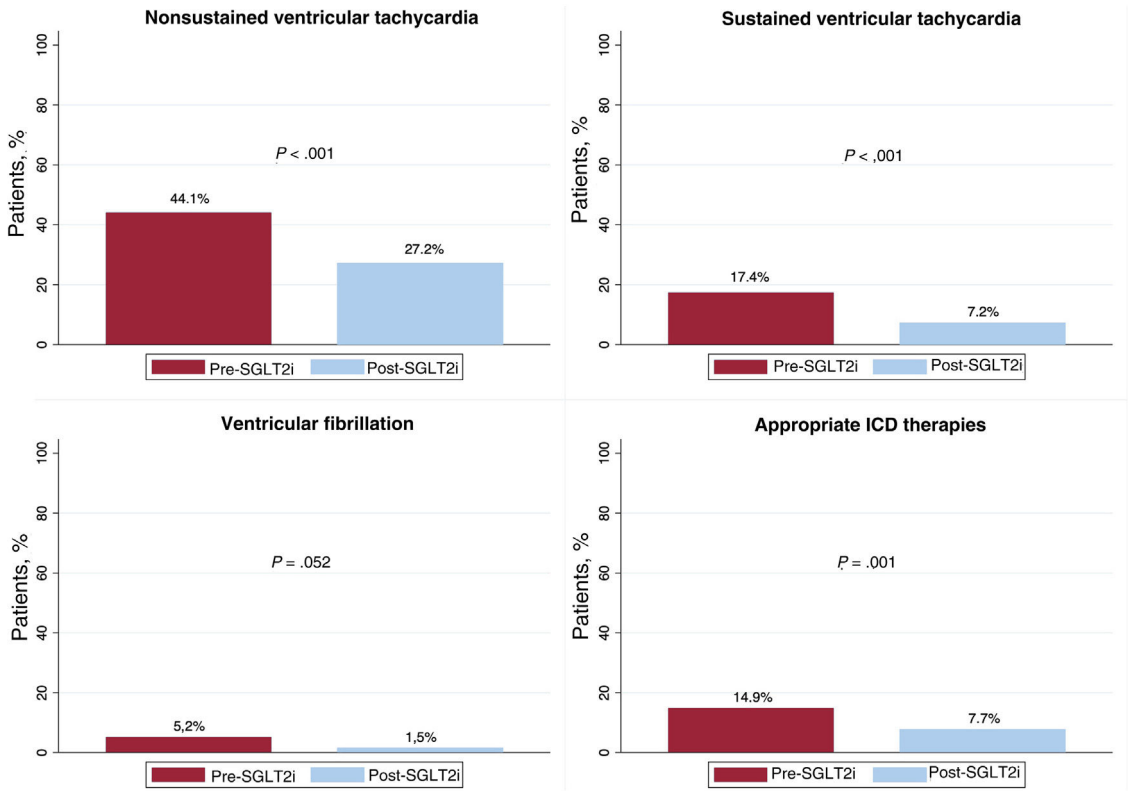

Figure 2. Percentages of patients with nonsustained ventricular tachycardia, sustained ventricular tachycardia, ventricular fibrillation, and appropriate ICD therapies in the 2 periods. ICD, implantable cardioverter-defibrillator; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

multivariate analysis was conducted for any AA, even though there was a slight but nonsignificant protective effect (OR = 0.70, 95%CI, 0.47-1.05, *P* = .087). A total of 112 patients (57.4%) in the pre-SGLT2i period and 129 (66.2%) in the post-SGLT2i period had available data on AF burden. Analysis of these data failed to reveal significant differences between the 2 periods (*P* = .097) (table 4).

DISCUSSION

This is the first study to assess the impact of treatment initiation with SGLT2i on the prevalence and incidence of AA and VA in the same cohort of patients with ICD in 2 follow-up periods, before and after SGLT2i initiation. The main findings of our study were the following: *a)* the number of patients with any type of VA or RVA

Table 3
Percentage of patients with ventricular arrhythmic events and their incidence in the 2 periods

Variable	Pre-SGLT2i	Post-SGLT2i	*P*
NSVT	86 (44.1)	53 (27.2)	< .01
Number of NSVT episodes per patient/y	2 [1-5]	1 [0-2]	< .01
SVT	34 (17.4)	14 (7.2)	< .01
Number of SVT episodes per patient/y	1 [1-3]	0 [0-2]	.046
VF	10 [5.2]	3 [1.5]	.052
Number of VF episodes per patient/y	1 [1-1]	0 [0-0]	.054
ATP	25 (12.8)	13 (6.7)	.023
Number of ATP episodes per patient/y	1 [0-3]	0 [0-2]	.045
Appropriate ICD discharge	13 (6.7)	6 (3.1)	.07
Number of episodes with appropriate ICD discharges per patient/y	1 [0-2]	0 [0-1]	.399
Appropriate ICD therapy	29 (14.9)	15 (7.7)	.011
Inappropriate ICD therapy	5 (2.6)	1 (0.5)	.103
Number of episodes with inappropriate ICD discharges per patient/y	1 [0.5-1]	0 [0-0.5]	.179
Any type of VA	102 (52.3)	59 (30.3)	< .001
Clinically relevant VA	42 (21.5)	17 (8.7)	< .001

ATP, antitachycardia pacing; ICD, implantable cardioverter-defibrillator; NSVT, nonsustained ventricular tachycardia; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SVT, sustained ventricular tachycardia; VA, ventricular arrhythmia; VF, ventricular fibrillation.
Data are expressed as No. (%) or median [interquartile range].

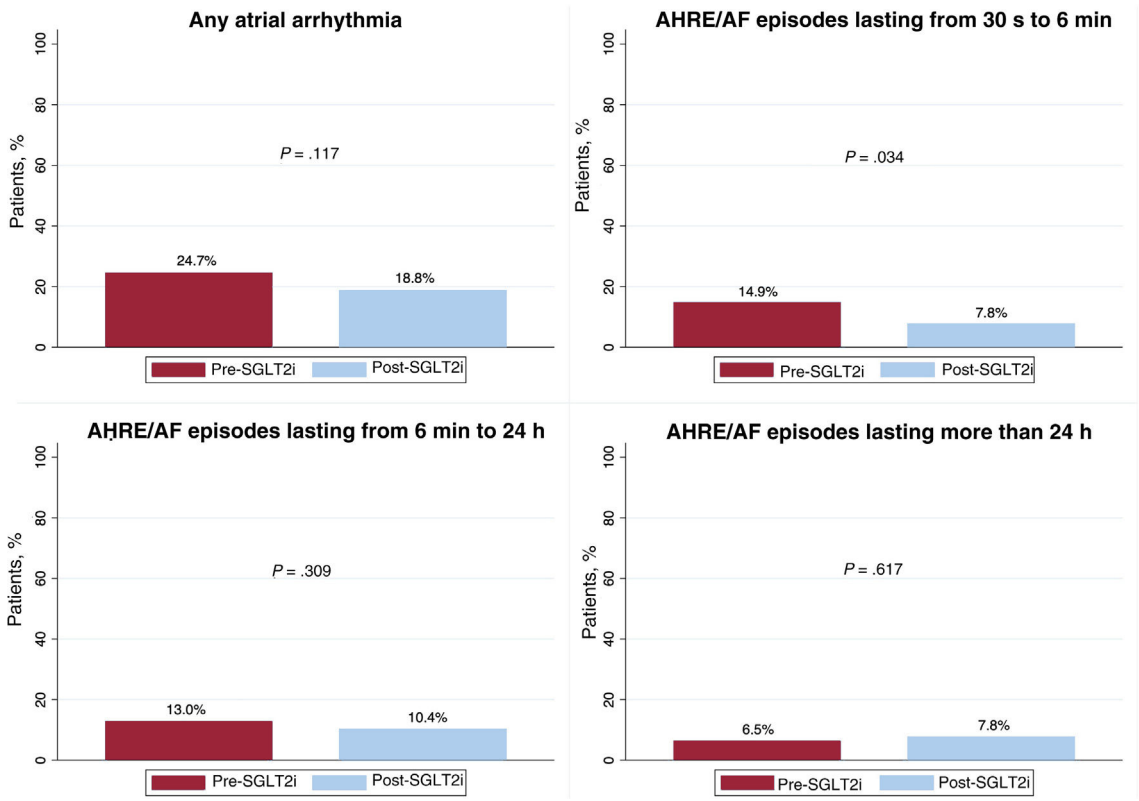

Figure 3. Percentages of patients with any atrial arrhythmia and episodes lasting from 30 seconds to 6 minutes, from 6 minutes to 24 hours, and for more than 24 hours. AF, atrial fibrillation; AHREs, atrial high-rate episodes; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

decreased after SGLT2i initiation; *b)* this decrease was due to a fall in the number of patients with NSVT, SVT, and appropriate ICD therapies, as well as a drop in the incidences of NSVT and SVT; and *c)* there were no differences in the number of AA episodes or in AF burden (figure 4).

Since the emergence of SGLT2is, substudies have linked their use to a lower incidence of AF and AA.[12,13] In a meta-analysis of 34 randomized studies including more than 60 000 patients with diabetes, SGLT2is were associated with a 19% reduction in AA incidence.[7] Another meta-analysis including patients with HF found a 25% decrease in the risk of AF events, both in patients with AF and without previous AF.[14] Nonetheless, other studies have obtained contradictory results. In a clinical practice study of patients with diabetes, although SGLT2i treatment was associated with a reduction in new-onset arrhythmias, this result was not significant when AF and supraventricular arrhythmias events were separately evaluated.[15] Along the same lines, a more recent meta-analysis of patients with HF found that SGLT2i treatment was not associated with a reduction in AA risk.[8] However, one of the main limitations of these studies is that only clinically relevant AAs were reported and the arrhythmia burden is unknown. In the only study to assess events in patients with a CIED, Younis et al. retrospectively evaluated the effect of SGLT2is on AA burden.[11] Their use was independently associated with a 15% reduction in the risk of AA and a fall in the number of events per year. However, as noted by the authors, although the results were adjusted by age, the patients receiving SGLT2i were younger, which means that the results need to be validated in prospective studies. In our study, despite a reduction in the number of patients with AA in the second period, the difference was not statistically significant (24.7% vs 18.8%, *P* = 117). In addition, no significant decrease was found in AF burden or in the incidence of AA episodes, despite a trend for protection in favor of SGLT2is (OR = 0.70; 95%CI, 0.47-105; *P* = .087). This lack of a benefit could be explained by the short

Table 4
Percentage of patients with atrial arrhythmic events, incidence and AF burden, excluding patients with permanent AF

Variable	Pre-SGLT2i (n = 154)	Post-SGLT2i (n = 154)	*P*
AHREs/AF episodes of 30 s-60 min	23 (14.9)	12 (7.8)	.034
Number of AHRE/AF episodes of 30 s-60 min per patient/y	1 [0-4]	0 [0-0]	.143
AHREs/AF episodes of 6 min-24 h	20 (13.0)	16 (10.4)	.371
Number of AHRE/AF episodes of 6 min-24 h per patient/y	2 [0.5-7]	1 [0-3]	.309
AHREs/AF episodes of > 24 h	10 (6.5)	12 (7.8)	.617
Number of AHRE/AF episodes of 6 min-24 h per patient/y	1 [0-1]	1 [0-2]	.843
Any AHRE/AF episode	38 (24.7)	29 (18.8)	.117
AF burden	0 [0-0.1]	0 [0-0]	.097

AF, atrial fibrillation; AHRE, atrial high-rate episode; SGLT2i, sodium-glucose cotransporter-2 inhibitor.
Data are expressed as No. (%) or median [interquartile range].

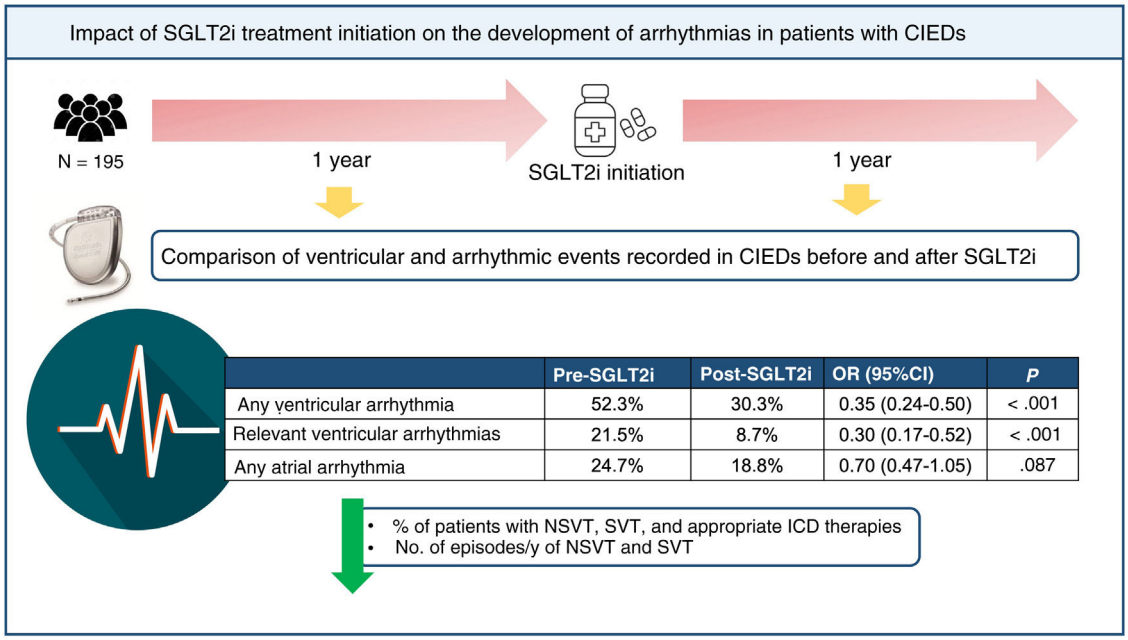

Figure 4. Central illustration. Impact of SGLT2i initiation on arrhythmic and ventricular events in patients with a CIED. CIED, cardiac implantable electronic device; NSVT, nonsustained ventricular tachycardia; OR, odds ratio; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SVT, sustained ventricular tachycardia.

follow-up period in our cohort and the low number of patients with an implanted atrial lead, which would have limited the monitoring of these events.

Analyses of the effect of SGLT2is on VA have linked these drugs to a reduction in SCD.[7] A study of more than 150 000 patients detected a fall in the risk of SCD vs other antidiabetic agents, although the decrease was not significant.[16] Another meta-analysis of 19 randomized studies also failed to find an association with a lower risk of VA.[9] However, a meta-analysis of 22 studies including more than 50 000 patients did find a reduction in VT risk, but not in cardiac arrest.[10] These discrepancies could be due to the heterogeneity of the included studies, as well as the low number of VAs recorded. Furthermore, a subanalysis of the DAPA-HF study reported an association between dapagliflozin therapy and a lower risk of the composite event of major VA, cardiac arrest, and SCD.[17] Nonetheless, this effect was not found in patients with a CIED or after separate analysis of VAs. Along these lines, a recent meta-analysis by Oates et al.[8] reported a decrease in SCD risk, but not in sustained VA.

However, as with the assessment of AAs, these studies only reported clinically relevant VAs and not asymptomatic VAs. In our study, the drop in VA was due to reductions in the percentages of patients with NSVT and SVT and in their incidence. These events are normally asymptomatic, particularly if they are effectively treated with APT; however, their onset and burden are associated with a worse prognosis.[18] Moreover, and in contrast to the findings of our cohort, the study by Younis et al. failed to detect a reduction in VA risk, despite finding a fall in mortality and AA risk. These discrepancies could be due to a higher percentage of patients with ICDs in our cohort, with higher arrhythmic risk, a situation reflected in the higher percentage of events recorded vs that study.

From the pathophysiological perspective, several SGLT2i mechanisms have been described that could exert antiarrhythmic properties. First, SGLT2is have been reported to inhibit Ca^{2+} currents by reducing Ca^{2+} kinase II/calmodulin-dependent activity, which decreases the release of Ca^{2+} from the sarcoplasmic reticulum and thereby reduces arrhythmogenesis due to delayed depolarizations.[19] The inhibition of late sodium currents has also been studied in murine models.[20] In addition, reverse remodeling and decreased interstitial fibrosis have been related to microre-entrant and macrore-entrant phenomena.[21,22] This effect, as well as the diuretic effects of SGLT2is, would reduce intracavitary pressures, which would decrease the parietal stress associated with the genesis of arrhythmic events.[23] Finally, they might have a modulatory effect on the autonomic nervous system in patients with HF.[24] Preclinical studies in mice have detected a possible inhibitory effect of the sympathetic nervous system due to a reduction in the renal concentrations of tyrosine hydroxylase and renal and cardiac norepinephrine.[25] In addition, in the EMBODY trial, which randomized empagliflozin or placebo to 105 patients with diabetes after an acute myocardial infarction,[26] there was improved autonomic nervous system activity, as evidenced by higher heart rate variability with SGLT2i, reflecting a greater parasympathetic balance.

Despite the above, much remains unknown concerning the effects of these drugs on arrhythmic events. However, various randomized studies are underway, such as the ERASe (NCT04600921)[27] and DAPA-AF (NCT04792190)[28] trials, which are assessing the impact of ertugliflozin and dapagliflozin on arrhythmic events in patients with a CIED.

Limitations

Our study contains certain limitations due to its design and retrospective nature. One of the main limitations is inherent to the selection bias caused by the exclusion of patients with at least 1 year of follow-up, which excludes those who died during this period. For this reason, the conclusions of this study cannot be generalized to patients with a worse functional class or who die soon after SGLT2i initiation. In addition, upon application of the recommendations of the latest clinical practice guidelines, the second period showed an increase in the proportion of patients under treatment with ARNI, a drug that has been associated with a decrease in arrhythmic events.[29] However, a subanalysis excluding patients who switched medication reached the same conclusions,

despite the sample size decrease. Furthermore, the treatment for HF was defined categorically and dose adjustments were not considered, meaning that the impact of the total dose on the outcomes could not be evaluated. In addition, the left ventricular ejection fraction was recorded at study inclusion and conclusions could not be reached regarding the dynamic changes during this period. Moreover, 19.5% of the cohort did not have complete remote monitoring and data may have been lost from these patients; however, data collection in the clinic was exhaustive and just 9.7% of patients had no remote monitoring in either period. Additionally, no analysis by sex was performed due to the low percentage of women (18.5%) included in the study. Finally, follow-up after SGLT2i initiation had a duration of 1 year, meaning that longer-term conclusions could not be made.

CONCLUSIONS

In conclusion, SGLT2i initiation in our cohort patients with an ICD or CRT-ICD was associated with a reduction in VAs and RVAs vs the pretreatment period. This reduction was due to falls in the percentages of patients with NSVT, SVT, and appropriate ICD therapies and in the incidences of NSVT and SVT. SGLT2i initiation was not accompanied by a reduction in AA in our study. However, prospective randomized studies are required to verify these conclusions.

WHAT IS KNOWN ABOUT THE TOPIC?

- Observational studies have linked SGLT2i use with a lower incidence of atrial fibrillation and sudden cardiac death.

WHAT DOES THIS STUDY ADD?

- SGLT2is may exert an antiarrhythmic effect and could decrease the risk of relevant ventricular arrhythmias in patients with cardiac implantable devices.

FUNDING

None.

ETHICAL CONSIDERATIONS

The study was approved by the local ethics committee of each center and all surviving patients at the time of analysis provided signed informed consent authorizing their participation.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

The authors of this manuscript declare that they did not use any artificial intelligence tool in the preparation of this manuscript.

AUTHORS' CONTRIBUTIONS

C. Minguito-Carazo, E. Sánchez Muñoz, M. Rodríguez Mañero, J.L. Martínez-Sande, M.L. Fidalgo Andrés, J. García Seara, J.M. González Rebollo, M. Rodríguez Santamarta, L. González Melchor, T. González Ferrero, L. Romero Roche, J.A. Fernández López, and E. Tundidor Sanz contributed to the data collection.

C. Minguito-Carazo and E. Sánchez Muñoz contributed to the statistical analysis.

C. Minguito-Carazo and E. Sánchez Muñoz contributed to the manuscript drafting.

C. Minguito-Carazo, E. Sánchez Muñoz, M. Rodríguez Mañero, J.L. Martínez-Sande, M.L. Fidalgo Andrés, J. García Seara, J.M. González Rebollo, M. Rodríguez Santamarta, L. González Melchor, T. González Ferrero, L. Romero Roche, J.A. Fernández López, E. Tundidor Sanz, F. Fernández Vázquez, and J.R. González-Juanatey contributed to the manuscript revision.

CONFLICTS OF INTEREST

No conflicts of interest.

ACKNOWLEDGMENTS

The authors appreciate the efforts of the nursing staff in charge of collecting arrhythmic event data in the clinic from the remote monitoring devices.

REFERENCES

1. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med.* 2019;381:1995–2008.
2. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. *N Engl J Med.* 2021;385:1451–1461.
3. Packer M, Anker SD, Butler J, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *N Engl J Med.* 2020;383:1413–1424.
4. Solomon SD, McMurray JJV, Claggett B, et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. *N Engl J Med.* 2022;387:1089–1098.
5. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J.* 2021;42:3599–3726.
6. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation.* 2022;145:E895–E1032.
7. Fernandes GC, Fernandes A, Cardoso R, et al. Association of SGLT2 inhibitors with arrhythmias and sudden cardiac death in patients with type 2 diabetes or heart failure: A meta-analysis of 34 randomized controlled trials. *Hear Rhythm.* 2021;18:1098–1105.
8. Oates CP, Santos-Gallego CG, Smith A, et al. SGLT2 inhibitors reduce sudden cardiac death risk in heart failure: Meta-analysis of randomized clinical trials. *J Cardiovasc Electrophysiol.* 2023;34:1277–1285.
9. Sfairopoulos D, Zhang N, Wang Y, et al. Association between sodium-glucose cotransporter-2 inhibitors and risk of sudden cardiac death or ventricular arrhythmias: a meta-analysis of randomized controlled trials. *EP Eur.* 2022;24:20–30.
10. Li HL, Lip GYH, Feng Q, et al. Sodium-glucose cotransporter 2 inhibitors (SGLT2i) and cardiac arrhythmias: a systematic review and meta-analysis. *Cardiovasc Diabetol.* 2021;20:1–13.
11. Younis A, Arous T, Klempfner R, et al. Effect of sodium glucose cotransporter 2 inhibitors on atrial tachy-arrhythmia burden in patients with cardiac implantable electronic devices. *J Cardiovasc Electrophysiol.* 2023;34:1595–1604.
12. Zelniker TA, Bonaca MP, Furtado RHM, et al. Effect of Dapagliflozin on Atrial Fibrillation in Patients with Type 2 Diabetes Mellitus: Insights from the DECLARE-TIMI 58 Trial. *Circulation.* 2020;141:1227–1234.
13. Li WJ, Chen XQ, Xu LL, Li YQ, Luo BH. SGLT2 inhibitors and atrial fibrillation in type 2 diabetes: a systematic review with meta-analysis of 16 randomized controlled trials. *Cardiovasc Diabetol.* 2020;19:1–14.
14. Pandey AK, Okaj I, Kaur H, et al. Sodium-glucose co-transporter inhibitors and atrial fibrillation: A systematic review and meta-analysis of randomized controlled trials. *J Am Heart Assoc.* 2021;10:e022222.
15. Chen HY, Huang JY, Siao WZ, Jong GP. The association between SGLT2 inhibitors and new-onset arrhythmias: A nationwide population-based longitudinal cohort study. *Cardiovasc Diabetol.* 2020;19:1–8.
16. Eroglu TE, Coronel R, Zuurbier CJ, Blom M, De Boer A, Souverein PC. Use of sodium-glucose cotransporter-2 inhibitors and the risk for sudden cardiac arrest and for all-cause death in patients with type 2 diabetes mellitus. *Eur Heart J Cardiovasc Pharmacother.* 2022;9:18–25.
17. Curtain JP, Docherty KF, Jhund PS, et al. Effect of dapagliflozin on ventricular arrhythmias, resuscitated cardiac arrest, or sudden death in DAPA-HF. *Eur Heart J.* 2021;42:3727–3738.

18. Samuel M, Elsokkari I, Sapp JL. Ventricular Tachycardia Burden and Mortality: Association or Causality? *Can J Cardiol.* 2022;38:454–464.
19. Mustroph J, Wagemann O, Lücht CM, et al. Empagliflozin reduces Ca/calmodulin-dependent kinase II activity in isolated ventricular cardiomyocytes. *ESC Hear Fail.* 2018;5:642–648.
20. Philippaert K, Kalyaanamoorthy S, Fatehi M, et al. Cardiac Late Sodium Channel Current Is a Molecular Target for the Sodium/Glucose Cotransporter 2 Inhibitor Empagliflozin. *Circulation.* 2021;143:2188–2204.
21. Santos-Gallego CG, Requena-Ibanez JA, San Antonio R, et al. Empagliflozin Ameliorates Diastolic Dysfunction and Left Ventricular Fibrosis/Stiffness in Nondiabetic Heart Failure: A Multimodality Study. *JACC Cardiovasc Imaging.* 2021;14:393–407.
22. Requena-Ibáñez JA, Santos-Gallego CG, Rodriguez-Cordero A, et al. Mechanistic Insights of Empagliflozin in Nondiabetic Patients with HFrEF: from the EMPA-TROPISM Study. *JACC Hear Fail.* 2021;9:578–589.
23. Gottlieb LA, Coronel R, Dekker LRC. Reduction in atrial and pulmonary vein stretch as a therapeutic target for prevention of atrial fibrillation. *Heart Rhythm.* 2023;20:291–298.
24. Lim VG, He H, Lachlan T, et al. Impact of sodium-glucose co-transporter inhibitors on cardiac autonomic function and mortality: no time to die. *EP Eur.* 2022;24:1052–1057.
25. Herat LY, Magno AL, Rudnicka C, et al. SGLT2 Inhibitor-Induced Sympathoinhibition: A Novel Mechanism for Cardiorenal Protection. *JACC Basic Transl Sci.* 2020;5:169–179.
26. Shimizu W, Kubota Y, Hoshika Y, et al. Effects of empagliflozin versus placebo on cardiac sympathetic activity in acute myocardial infarction patients with type 2 diabetes mellitus: The EMBODY trial. *Cardiovasc Diabetol.* 2020;19:1–12.
27. von Lewinski D, Tripolt NJ, Sourij H, et al. Ertugliflozin to reduce arrhythmic burden in ICD/CRT patients (ERASe-trial) - A phase III study. *Am Heart J.* 2022;246:152–160.
28. Use of Dapagliflozin to Reduce Burden of Atrial Fibrillation in Patients Undergoing Catheter Ablation of Symptomatic Atrial Fibrillation. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/study/NCT04792190. Accessed 3 May 2023.
29. Martens P, Nuyens D, Rivero-Ayerza M, et al. Sacubitril/valsartan reduces ventricular arrhythmias in parallel with left ventricular reverse remodeling in heart failure with reduced ejection fraction. *Clin Res Cardiol.* 2019;108:1074–1082.