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Effect of sacubitril/valsartan and SGLT2 inhibitors on arrhythmia burden in ICD patients

Fatih Öztürk^{1*} and Mehmet Yaman²

Abstract

Background This study aimed to examine whether the use of sodium–glucose co-transporter 2 inhibitors (SGLT2i) and/or sacubitril/valsartan in individuals with an implantable cardioverter-defibrillator (ICD) was associated with differences in pathological rhythm burden, specifically atrial fibrillation (AF), ventricular tachycardia (VT), and ventricular fibrillation (VF), during follow-up.

Methods Data from 275 patients who underwent ICD implantation between 2022 and 2025 were analyzed retrospectively. The primary endpoint was change in device-detected arrhythmic burden, categorized as unchanged/increased, 0–50% reduction, 50–100% reduction, or arrhythmia-free status during 12-month follow-up. The secondary endpoint was change in LVEF (Δ EF). Associations between medical therapies and EF change were assessed using multivariable linear regression models adjusted for demographic and clinical covariates.

Results Overall, mean LVEF increased significantly during follow-up (Δ EF $9.7 \pm 8.7\%$, $p < 0.001$). In adjusted analyses, ARNI use was independently associated with greater EF improvement ($B = 10.647$, $p < 0.001$), whereas SGLT2i therapy alone was not significantly associated with Δ EF. In unadjusted analyses, both ARNI and SGLT2i therapies were associated with a higher likelihood of substantial reduction in arrhythmic burden and arrhythmia-free status ($p < 0.001$ for both). Patients receiving combined ARNI and SGLT2i therapy demonstrated the highest proportion of arrhythmia-free status during follow-up.

Conclusion In this retrospective cohort of ICD recipients with HFrEF, ARNI therapy was independently associated with greater improvement in LVEF, while both ARNI and SGLT2i use were associated with lower device-detected arrhythmic burden in unadjusted analyses. Prospective studies are required to determine causality and clarify the independent antiarrhythmic effects of contemporary guideline-directed therapies in ICD populations.

Keywords heart failure, implantable cardioverter-defibrillators, sacubitril/valsartan, SGLT2i

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Introduction

Heart failure (HF) remains a major cause of morbidity and mortality worldwide despite advances in pharmacological and device-based therapies [1–3]. Recently, SGLT2 inhibitors (SGLT2i) have become a significant therapeutic option for HF management, with significant reductions in mortality and improvements in quality of life [4]. As evidenced by the PARADIGM-HF trial, the administration of sacubitril/valsartan was associated with a lower risk of sudden cardiac death (SCD) [5]. Accumulating evidence suggests that this therapy may exert antiarrhythmic effects through both direct electrophysiological mechanisms and indirect pathways mediated by favorable left ventricular remodeling [6]. Emerging evidence suggests that the combined use of SGLT2i and sacubitril/valsartan may be associated with reductions in arrhythmic events in patients with HF; however, data specifically derived from device-detected arrhythmia monitoring remain limited [7–9].

Despite the growing body of evidence from randomized trials and large observational studies suggesting antiarrhythmic benefits of ARNI and SGLT2i, data derived from real-world ICD interrogation remain limited. The present study adds to the literature by evaluating device-detected arrhythmic burden alongside changes in left ventricular ejection fraction within a contemporary cohort of ICD recipients undergoing GDMT optimization. Furthermore, by examining the combined use of ARNI and SGLT2i, this study provides additional insight into their potential synergistic association with arrhythmia-free status in routine clinical practice.

ICD therapy represents a cornerstone in the prevention of sudden cardiac death among patients with HFrEF. Accordingly, the observed arrhythmic burden in ICD recipients reflects not only the intrinsic disease substrate but also device-related factors. Contemporary international guidelines strongly recommend ICD implantation as a Class I indication for primary prevention in patients with LVEF $\leq$ 35% despite optimal medical therapy [10, 11]. Although ICDs terminate life-threatening arrhythmias, they do not modify the underlying arrhythmogenic substrate. Therefore, the observed arrhythmic burden in ICD recipients reflects not only the intrinsic disease substrate but also device-related factors. A decline in quality of life and less favorable clinical results has been observed with repeated interventions involving ICD [3, 12].

At the same time, guideline-directed medical therapy (GDMT) for HF has evolved considerably. Optimization of contemporary pharmacotherapy before and after ICD implantation may promote reverse remodeling and modulate arrhythmic risk [13]. However, the extent to which newer therapies, particularly angiotensin receptor–neprilysin inhibitors (ARNI) and SGLT2i, influence

device-detected arrhythmias in ICD recipients remains incompletely defined.

Although prior studies have evaluated the individual effects of ARNI or SGLT2i on ventricular remodeling and clinical arrhythmic outcomes, data on their impact on device-detected arrhythmia burden in patients with established ICD therapy remain sparse, especially regarding the potential additive effect of combined therapy in real-world cohorts. Rather than re-establishing the efficacy of these therapies, the present study sought to provide real-world observational evidence in ICD recipients receiving contemporary guideline-directed medical therapy by evaluating whether ARNI and SGLT2i use, either alone or in combination, was associated with changes in device-detected arrhythmic burden and left ventricular systolic function over follow-up.

Methods

This retrospective single-center cohort study included adult patients with HFrEF who had already undergone ICD implantation between January 2022 and December 2025 and who had available baseline and follow-up clinical, echocardiographic, and device interrogation data. The study assessed associations between exposure to contemporary guideline-directed medical therapy, particularly sacubitril/valsartan (ARNI) and SGLT2i, and subsequent changes in device-detected arrhythmic burden and LVEF during follow-up. All comparisons were made within the same observational cohort according to treatment exposure status; no separate control group was used. Ethical approval for retrospective analysis of anonymized patient records was obtained from the Zonguldak Bülent Ecevit University Ethics Committee (Approval No: 2025/17; Date: 01 October 2025), prior to data extraction and statistical analysis. As the study involved retrospective review of existing medical records, the requirement for written informed consent was waived by the ethics committee. In this retrospective cohort, all included patients had a previously implanted ICD and were subsequently followed after initiation or optimization of guideline-directed medical therapy (GDMT), including ARNI and/or SGLT2i. Therefore, comparisons between ‘users’ and ‘non-users’ reflect treatment exposure within the same cohort rather than separate control groups.

Consecutive patients were screened for eligibility. Patients were required to be 18 years of age or older, to have complete medical records and ICD interrogation data, and to have at least 12 months of follow-up after initiation or optimization of GDMT were included in the study. Furthermore, the availability of both baseline and follow-up echocardiographic measurements was a requirement for the final assessment. The study excluded individuals who were pregnant, had end-stage renal disease requiring dialysis, had chronic liver disease,

had active malignancy, or had familial hyperlipidemia. A total of 27 patients were excluded due to incomplete records, missing device interrogation data, or insufficient follow-up.

The primary exposure variables were treatment with sacubitril/valsartan (ARNI) and SGLT2i. Individual titration of sacubitril/valsartan doses was performed based on blood pressure, renal function, and general tolerability. SGLT2i use was recorded separately. Patients were categorized according to ARNI use, SGLT2i use, and combined ARNI plus SGLT2i therapy. The medical records also noted the presence of several cardiovascular medications, including ACE inhibitors, angiotensin receptor blockers, beta-blockers, mineralocorticoid receptor antagonists, diuretics, antiplatelet agents, and oral anticoagulants.

Individualized ICD programming was conducted in accordance with standardized institutional protocols, which were based on specific heart rate detection zones. All patients in the study had dual-chamber ICD devices implanted; no patients with single-chamber ICD or CRT-D systems were included. For VF (≥ 200 bpm), the programmed therapy involved anti-tachycardia pacing during the charging sequence, followed by a high-energy shock. The detection intervals were set from 30 to 40 beats to minimize inappropriate therapy. For VT below 170 beats per minute, arrhythmias were primarily monitored, with anti-tachycardia pacing delivered when clinically indicated. Algorithms for discriminating supra-ventricular tachycardia were activated across all devices, the initial shock energy was set to maximum output, and systems for monitoring lead integrity were activated.

ICD interrogation data underwent review at three-month intervals throughout a 12-month follow-up period. Arrhythmic events were assessed during the period prior to treatment optimization and throughout the subsequent 12 months. The primary arrhythmic results consisted of the cumulative rate of VT, total VF events, non-sustained VT (characterized by four or more consecutive beats lasting under thirty seconds), VF, atrial tachyarrhythmias, AF, and suitable ICD treatments, including anti-tachycardia pacing and defibrillation shocks. Arrhythmia burden was categorized according to percentage reduction during follow-up. VT not monitored' refers to patients in whom ventricular tachycardia detection zones were not actively programmed or in whom clinically relevant VT episodes were not captured during device interrogation. In addition to relative changes, absolute numbers of arrhythmic events were recorded during follow-up; however, the primary analysis focused on percentage change in burden to account for inter-individual variability in baseline arrhythmia frequency.

The clinical evaluation for all participants included a physical examination, a medication review, and a standard 12-lead electrocardiogram. After resting for at least 15 min, transthoracic echocardiography was conducted in the left lateral decubitus position using a Vivid E9 system (General Electric Medical Systems, Milwaukee, WI, USA) equipped with an X5-1 probe. Measurements using two-dimensional, M-mode, and Doppler techniques were taken from parasternal and apical perspectives, in line with the recommendations of the European Association of Echocardiography [14]. At both the initial visit and the follow-up, the left ventricular EF (LVEF) was assessed. The difference between the final and baseline EF values was then determined, yielding the change in ejection fraction (Δ EF). Treatment exposure was determined on clinical grounds, with careful consideration of individual patient characteristics and treatment suitability.

Statistical method

Statistical analyses were performed using IBM SPSS Statistics for MacOS, version 30.0 (IBM Corp., Armonk, NY, USA). Normality for continuous variables was evaluated through the Shapiro–Wilk test. Categorical variables are presented as counts and percentages (n,%). Continuous variables are expressed as mean $\pm$ standard deviation when normally distributed, and as median with inter-quartile range (IQR) when nonnormally distributed. Paired t-tests were administered for dependent measures, with Student's or Welch's t-test selected for inter-group comparisons based on distributional assumptions. The chi-square test was employed to compare the relationships between different categories within the data. The association between predictors and Δ EF was assessed using multivariate linear regression. The development of the regression models was conducted in three phases: Model 1 comprised only treatment variables, Model 2 integrated demographic and clinical variables, and Model 3 accounted for supplementary cardiac treatments. VIF and tolerance values were employed to assess multicollinearity among the independent variables, and this analysis found no significant collinearity. Statistically significant results were defined as those with a p-value less than 0.05.

Results

A total of 275 patients were included in the final analysis. The mean age of the cohort was 62.0 ± 13.8 years, and 50.9% were male. Diabetes mellitus (58.5%), coronary artery disease (54.2%), and hypertension (45.1%) were the most frequently observed comorbidities. At baseline, 69.8% of the patient cohort had no documented history of paroxysmal atrial fibrillation (PAF), 18.5% had experienced PAF that later resolved, and 11.6% had persistent AF. The mean baseline LVEF was $30.7 \pm 8.0\%$,

Table 1 The demographic and clinical characteristics of participants

Variables	Total n (%) n = 275	Variables	Total n (%) n = 275
Sex		HT	124 (45.1)
Male	140 (50.9)	DM	161 (58.5)
Female	135 (49.1)	Smoker	79 (28.7)
Age (years)*	62.0 ± 13.8	AF	
GFR (ml/s/1.73 m ²)*	83.8 ± 37.1	PAF and then corrected	51 (18.5)
Laboratory data		No PAF	192 (69.8)
LDL (mg/dL)*	116.0 ± 35.8	AF continues	32 (11.6)
Glucose (mg/dL)*	107 (92–147)	First EF*	30.7 ± 8.0
AST (U/L)*	28 (18–40)	Last EF*	40.4 ± 9.0
Creatinine (mg/dL)*	0.9 (0.8–1.2)	ΔEF*	9.7 ± 8.7
Potassium (meq/L)*	4.3 (4–4.7)	Percentage reduction in VT/VF	
Sodium (meq/L)*	139.0 (137–142)	Unchanging/increasing	30 (10.9)
Hgb (g/dL)*	13.6 (12.8–14.9)	0%–50% decreasing	80 (29.1)
Comorbidities		50%–100% decreasing	105 (38.2)
CAD	149 (54.2)	Without analyzable VT monitoring data	60 (21.8)

*Numeric variables were presented as median (interquartile range [IQR]) or mean ± SD

Abbreviations: eGFR estimated glomerular filtration rate, HT Hypertension, DM Diabetes, LDL Low Density Lipoprotein, HDL High Density Lipoprotein, EF Ejection fraction, AF Atrial Fibrillation, PAF Paroxysmal atrial fibrillation, VF ventricular fibrillation, VT Ventricular tachycardia

which increased to $40.4 \pm 9.0\%$ at follow-up, corresponding to a mean ΔEF of $9.7 \pm 8.7\%$. Detailed demographic, laboratory, and clinical characteristics are summarized in Table 1.

Regarding the prevalence of ventricular arrhythmias, 38.2% of individuals experienced a 50–100% reduction in VT/VF during the follow-up period, while 29.1% exhibited a 0–50% reduction. Arrhythmia burden remained unchanged or increased in 10.9% of patients, and 21.8% were not under VT monitoring (Table 1).

The study revealed a substantial increase in LVEF across all participants after medical therapy ($p < 0.001$), as detailed in Table 2. A significantly lower baseline EF was noted in patients receiving ARNI therapy compared to non-users ($28.9 \pm 7.1\%$ vs. $33.0 \pm 8.5\%$), and they exhibited a markedly greater increase in EF during the follow-up period ($14.9 \pm 7.0\%$ vs. $3.1 \pm 5.7\%$, $p < 0.001$). Final EF values were also significantly higher in ARNI users ($43.8 \pm 7.7\%$ vs. $36.0 \pm 8.8\%$, $p < 0.001$). Conversely, SGLT2i therapy alone did not demonstrate statistically significant variations in baseline EF, final EF, or ΔEF (all $p > 0.05$). However, a significantly greater improvement in EF was observed in patients undergoing combined ARNI and SGLT2i therapy when compared to individuals not receiving combination therapy (ΔEF : $14.7 \pm 7.0\%$ vs. $6.4 \pm 8.2\%$, $p < 0.001$).

Multivariate linear regression analysis evaluating predictors of ΔEF is presented in Table 3. When considering only treatment variables in Model 1, ARNI use showed an independent and positive association with EF improvement ($B = 11.137$, $p < 0.001$), whereas SGLT2i and combined therapy were not significant predictors. In Model 2, following adjustments for demographic variables and baseline EF, ARNI remained a strong independent predictor of ΔEF ($B = 10.365$, $p < 0.001$). Concurrently, baseline EF exhibited a negative association with EF change

Table 2 Distribution of Ejection Fraction (EF) Measurements of Patients Before and After Treatment

Medication	First EF Mean + SD	p	Last EF Mean + SD	p	Delta EF Mean + SD	p
All patients	30.7 ± 8.0		40.4 ± 9.0		9.7 ± 8.7	< 0.001*
ARNI		< 0.001**		< 0.001***		< 0.001**
Non- users	33.0 ± 8.5		36.0 ± 8.8		3.1 ± 5.7	
Users	28.9 ± 7.1		43.8 ± 7.7		14.9 ± 7.0	
SGLT2i		0.314**		0.863***		0.483***
Non- users	30.0 ± 7.3		40.3 ± 9.4		10.3 ± 8.7	
Users	31.0 ± 8.3		40.5 ± 8.9		9.5 ± 8.8	
ARNI+SGLT2i		0.005***		< 0.001**		< 0.001**
Non- users	31.8 ± 8.2		38.2 ± 9.2		6.4 ± 8.2	
Users	29.0 ± 7.4		43.7 ± 7.7		14.7 ± 7.0	

* Paired t-test

** Welch t-test

*** Student's t-test

Abbreviations: ARNI angiotensin receptor neprilysin inhibitor (Sacubitril/valsartan), SGLT-2i, sodium-glucose cotransporter inhibitors

Table 3 Multivariate Linear Regression Analysis of Factors Associated with Ejection Fraction Change (Δ EF) in Patients

Model		B	Standard Error	Beta	t	p-value
Model 1	ARNI	11.137	1.409	0.635	7.902	<0.001
	SGLT2i	-1.795	1.253	-0.095	-1.433	0.153
	Combined	1.057	1.695	0.059	0.624	0.533
Model 2	ARNI	10.365	1.333	0.591	7.774	<0.001
	SGLT2i	-1.198	1.183	-0.063	-1.013	0.312
	Combined	0.105	1.617	0.006	0.065	0.948
	Age	-0.015	0.027	-0.024	-0.568	0.570
	Sex	-0.543	0.748	-0.031	-0.727	0.468
	Smoker	-1.556	0.837	-0.081	-1.858	0.064
	First EF	-0.292	0.048	-0.268	-6.097	<0.001
Model 3	ARNI	10.647	1.629	0.607	6.535	<0.001
	SGLT2i	-1.357	1.235	-0.072	-1.099	0.273
	Combined	0.296	1.665	0.017	0.178	0.859
	Age	-0.014	0.027	-0.023	-0.535	0.593
	Sex	-0.649	0.754	-0.037	-0.861	0.390
	Smoker	-1.178	0.872	-0.061	-1.352	0.178
	First EF	-0.293	0.048	-0.269	-6.090	<0.001
	ACEI/ARB	0.415	1.462	0.023	0.284	0.777
	Beta-blocker	-2.737	1.574	-0.131	-1.739	0.083
	NOAC	-1.142	1.089	-0.060	-1.049	0.295
	ASA	2.839	1.383	0.152	2.053	0.041
	P2Y12 inhibitor	-0.730	0.777	-0.041	-0.939	0.348
	Diuretic	0.294	0.820	0.016	0.358	0.721
	Spironolactone	-0.190	0.812	-0.011	-0.235	0.815

* Independent variables: Delta EF

Abbreviations: ARNI angiotensin receptor neprilysin inhibitor (Sacubitril/valsartan), ACEI angiotensin-converting enzyme inhibitor, ARB angiotensin II receptor antagonist, Betbloc Beta blocker, NOAC Non-Vitamin K Antagonist Oral Anticoagulant, ASA acetylsalicylic acid, SGLT-2i sodium-glucose cotransporter inhibitors. Statistically significant results are indicated by bold font

($B = -0.292$, $p < 0.001$), indicating greater improvement among patients with lower initial EF. These associations persisted in the fully adjusted Model 3, which additionally accounted for concomitant cardiac medications. Within this model, ARNI therapy remained independently associated with EF increase ($B = 10.647$, $p < 0.001$), and ASA administration demonstrated a modest but statistically significant relationship with Δ EF ($p = 0.041$).

As shown in Table 4, medical therapies influence the distribution of rhythm disorders. A notable association was observed between ARNI therapy and improved arrhythmia outcomes ($p < 0.001$). A significantly higher percentage of ARNI users experienced complete arrhythmia freedom compared to non-users (31.8% vs. 9.1%), with ARNI users also showing a greater reduction in arrhythmia burden (50–100%). Similarly, SGLT2i therapy was associated with a significantly greater reduction in arrhythmia burden ($p < 0.001$), with 27.7% of users achieving arrhythmia-free status compared with 8.3% of non-users.

The most significant improvement in arrhythmia was seen in patients receiving combined ARNI and SGLT2i treatments ($p < 0.001$), with 38.5% achieving arrhythmia-free status. While Non-Vitamin K Antagonist Oral

Anticoagulant therapy correlated with a significant enhancement in heart rhythm ($p = 0.034$), other treatments such as beta-blockers, ASA, P2Y12 inhibitors, diuretics, and spironolactone did not show a significant association with changes in the severity of arrhythmias.

Discussion

In this single-center retrospective cohort study of 275 patients with HFrEF who had undergone ICD implantation, we investigated the relationship between current GDMT specifically sacubitril/valsartan (ARNI) and SGLT2i, and subsequent alterations in left ventricular systolic function and device-detected arrhythmic burden during follow-up. Our findings should be interpreted as complementary real-world evidence and hypothesis-generating rather than as proof of independent antiarrhythmic efficacy. Overall, LVEF improved significantly across the cohort. ARNI therapy demonstrated an independent correlation with enhanced EF and a substantial decrease in arrhythmia burden. Concurrently, SGLT2i use was significantly linked to favorable arrhythmic outcomes, especially when combined with ARNI therapy. Patients receiving combined ARNI and SGLT2i therapy demonstrated the highest proportion of favorable arrhythmic

Table 4 Distribution of Rhythm Disorder Changes According to Medical Treatments of the Participants

Medications	Rhythm disorder change				p-value
	Unchanged/Increased	0–50% Decrease	50–100% Decrease	No Arrhythmia	
ARNI, n (%)					< 0.001
Non- users	20 (16.5)	48 (39.7)	42 (34.7)	11 (9.1)	
Users	10 (6.5)	32 (20.8)	63 (40.9)	49 (31.8)	
SGLT2i, n (%)					< 0.001
Non- users	20 (23.8)	32 (38.1)	25 (29.8)	7 (8.3)	
Users	10 (5.2)	48 (25.1)	80 (41.9)	53 (27.7)	
ARNI+SGLT2i, n (%)					< 0.001
Non- users	24 (14.5)	61 (36.7)	63 (38)	18 (10.8)	
Users	6 (5.5)	19 (17.4)	42 (38.5)	42 (38.5)	
ACEI/ARB, n (%)					< 0.001
Non- users	24 (13.5)	36 (20.2)	69 (38.8)	49 (27.5)	
Users	6 (6.2)	44 (45.4)	36 (37.1)	11 (11.3)	
BBLOC, n (%)					0.311
Non- users	6 (9.7)	22 (35.5)	18 (29)	16 (25.8)	
Users	24 (11.3)	58 (27.2)	87 (40.8)	44 (20.7)	
NOAC, n (%)					0.034
Non- users	26 (13.5)	52 (27.1)	78 (40.6)	36 (18.8)	
Users	4 (4.8)	28 (33.7)	27 (32.5)	24 (28.9)	
ASA, n (%)					0.599
Non- users	8 (9.1)	29 (33)	30 (34.1)	21 (23.9)	
Users	22 (11.8)	51 (27.3)	75 (40.1)	39 (20.9)	
P2Y12, n (%)					0.394
Non- users	20 (12.6)	46 (28.9)	55 (34.6)	38 (23.9)	
Users	10 (8.6)	34 (29.3)	50 (43.1)	22 (19)	
Diuretics, n (%)					0.825
Non- users	12 (12.6)	25 (26.3)	36 (37.9)	22 (23.2)	
users	18 (10)	55 (30.6)	69 (38.3)	38 (21.1)	
Spinelactone, n (%)					0.346
Non- users	12 (10.3)	40 (34.2)	44 (37.6)	21 (17.9)	
Users	18 (11.4)	40 (25.3)	61 (38.6)	39 (24.7)	

Abbreviations: ARNI angiotensin receptor–neprilysin inhibitors (Sacubitril/valsartan), SGLT2i Sodium-glucose Cotransporter-2 Inhibitors, ACEI Angiotensin-converting enzyme inhibitors, ARB Angiotensin receptor blocker, Bbloc Beta blocker, NOAC Non-Vitamin K Antagonist Oral Anticoagulant, ASA acetylsalicylic acid. Statistically significant results are indicated by bold font

profiles in unadjusted analyses; however, these findings should be interpreted cautiously given the observational design and potential treatment-selection bias. Despite the limitations of retrospective design precluding causal inference, the results of the current study indicate that optimization of contemporary medical treatments for individuals with ICDs could facilitate reverse remodeling and significantly decrease device-detected arrhythmic episodes.

Sacubitril/valsartan is a cornerstone therapy in the guideline-directed medical treatment of HFrEF. The PARADIGM-HF trial showed a significant decrease in cardiovascular and HF-related deaths among patients with HFrEF [5, 15, 16]. Considering the adverse cardiac remodeling effects associated with sacubitril/valsartan, prior observational studies documented enhancements in echocardiographic findings after initiation of drug treatment [17–19]. The present study indicated that

patients on sacubitril/valsartan achieved a significantly greater increase in LVEF compared with non-users. Arrhythmic outcomes were also systematically evaluated during follow-up. These results suggest a significant correlation between ARNI treatment and improved systolic function, potentially due to beneficial reverse remodeling in patients receiving the therapy. Notwithstanding the clinical relevance of the observed increase in EF, which points to improved ventricular performance, the study was not designed to assess whether these changes translate into reductions in long-term mortality or morbidity. Recent data also support a potential autonomic mechanism underlying these effects. A 2026 study using ICD-derived physiological data demonstrated that sacubitril/valsartan may improve cardiac autonomic function and reduce ventricular arrhythmias, further supporting the observed associations in our cohort [20].

Large-scale randomized trials involving patients with type 2 diabetes have consistently shown that SGLT2i significantly reduce hospitalizations for HF [20]. No statistically significant difference in EF was observed in the present study concerning SGLT2i use. Given the unavailability of symptom status and clinical endpoints (e.g., NYHA class, NT-proBNP, or HF hospitalization), an evaluation of the association between SGLT2i use and symptomatic improvement could not be performed.

Paolo Basile et al. [21] documented a non-statistically significant decline in Major Adverse Arrhythmic and Cardiovascular Events (MAACE) among chronic HF patients after six months of SGLT2i therapy. Numerous studies and meta-analyses have consistently demonstrated that SGLT2i reduce the risk of AF and VT [7, 22, 23]. Mariani et al. showed that SGLT2i decreased the probability of AF recurrence [24]. In the present study, the incidence of ventricular arrhythmias was significantly lower among patients receiving SGLT2i therapy compared with those not treated with these agents, suggesting a potential protective association between SGLT2i use and ventricular arrhythmic burden during follow-up. However, contrary to prior reports, no significant change in PAF was observed, which may be explained by the limited sample size and the presence of advanced left atrial fibrosis commonly seen in patients with HF.

In the PARADIGM-HF study, sacubitril/valsartan was shown to lower the likelihood of SCD [5]. Subsequent studies have provided data that lends support to the concept of an antiarrhythmic effect [6]. Although several experimental and translational studies have proposed potential molecular mechanisms through which neprilysin inhibition may influence myocardial remodeling and electrophysiological stability, the present study was not designed to evaluate mechanistic pathways. Therefore, any biological explanation for the observed associations remains speculative [9]. Previous observational studies have documented a decrease in ventricular arrhythmias identified by ICDs, specifically regarding the frequency of VT/VF and ICD interventions and this reduction extends to non-sustained VT, VT, premature ventricular contractions, and the occurrence of appropriate ICD shocks [8, 12]. In the present study, sacubitril/valsartan therapy was associated with a significant reduction in ventricular arrhythmic events. Although the reduction in arrhythmic burden occurred in parallel with improvements in LVEF, the study design does not allow determination of whether EF improvement mediated arrhythmic changes.

The findings of the present study suggest an association between combined sacubitril/valsartan and SGLT2i therapy and improved arrhythmic outcomes. Combined therapy was associated with greater improvement in arrhythmic outcomes. Patients who received optimized medical therapy exhibited enhanced EF, and a decreased

arrhythmic burden post-implantation, highlighting the dynamic nature of frequently tracked parameters following ICD implantation. These findings may be clinically relevant for patients with heart failure who are relatively older and medically vulnerable in routine practice, as optimization of evidence-based therapies may remain incomplete because of comorbidity burden, tolerability concerns, renal function, or blood pressure limitations. Although our study was not designed as an age-stratified analysis and the mean age of the cohort was 62.0 ± 13.8 years, the observed associations between contemporary GDMT exposure and more favorable echocardiographic and arrhythmic profiles support the importance of careful medical optimization across a broad HFrEF population, particularly in patients with greater clinical complexity.

Prior to ICD implantation, patients with HFrEF are generally recommended to receive at least three months of optimized guideline-directed medical therapy to facilitate reverse remodeling and improve LVEF, with ICD placement considered in those who continue to have an $LVEF \leq 35\%$, a timeframe that reflects both uncertainty regarding the duration required for meaningful remodeling and concern about ongoing arrhythmic risk during treatment optimization. Notably, the currently recommended duration of GDMT in HFrEF is largely based on earlier studies conducted in an era when available therapies had comparatively modest effects on reverse remodeling, with the most pronounced improvements typically occurring during the early phase after treatment initiation [13]. While EF trajectories may evolve with optimized GDMT, the present study does not provide evidence to support modifications in ICD implantation timing or eligibility criteria. However, further prospective trials are necessary before modifications to ICD decision-making should be considered.

A recent analysis using physiological data obtained from implantable cardioverter-defibrillators reported that sacubitril/valsartan therapy was associated with favorable changes in cardiac autonomic function in patients with HFrEF, further supporting the hypothesis that ARNI may influence arrhythmic susceptibility through mechanisms beyond reverse remodeling alone. Our findings are directionally consistent with this device-based literature; however, unlike that study, we did not assess autonomic markers directly, and therefore mechanistic interpretation remains limited [25].

The initial point is that contemporary GDMT has been observed to prolong the period of adverse cardiac remodeling, extending significantly beyond 90 days. Moreover, a significant proportion of patients might experience considerable enhancement in LVEF for a duration extending up to twelve months post-treatment modifications [26, 27]. The results of the present study

indicated that the most effective treatment regimen led to a lower incidence of arrhythmia and an improved EF. A proportion of patients demonstrated EF improvement beyond conventional guideline thresholds during follow-up; however, all patients in this cohort had already undergone ICD implantation, and these observations should not be interpreted as evidence against guideline-based device therapy. The observed associations between contemporary GDMT and both EF improvement and arrhythmic burden reduction warrant further investigation in prospective studies designed to evaluate causality. These findings may be particularly relevant in older and clinically vulnerable patients, in whom optimization of GDMT is often limited and heart failure hospitalizations tend to be more complex and prolonged.

This study has several limitations. The retrospective, single-center design precludes causal inference. An important consideration is that a proportion of patients demonstrated substantial improvement in LVEF during follow-up, potentially exceeding guideline thresholds for primary prevention ICD implantation. This may reflect suboptimal medical therapy at the time of implantation, a common real-world limitation in retrospective cohorts. Furthermore, the absence of randomization in treatment groups, with patients receiving ARNI notably exhibiting lower baseline EF and potentially benefiting from more aggressive GDMT optimization, suggests a possibility of confounding by indication. The marked improvement in LVEF during follow-up raises the possibility that some patients were not yet fully optimized on contemporary GDMT at the time of ICD implantation. However, because of the retrospective observational design, we cannot determine whether earlier or more complete pre-implant optimization would have altered ICD eligibility in individual cases. Individualized ICD programming, as done in this study, could have influenced both the detected burden of arrhythmias and the therapies that were delivered. However, all patients had dual-chamber ICD devices, which reduces potential heterogeneity related to device type. The evaluation of arrhythmia outcomes did not incorporate time-dependent methodologies, and the absence of clinical heart failure endpoints, such as NYHA class, NT-proBNP levels, and heart failure hospitalizations, restricted the mechanistic interpretation of symptom-related effects. Therefore, large-scale, prospective, randomized studies incorporating standardized device programming and comprehensive clinical endpoints are warranted to further clarify the causal relationships and underlying mechanisms.

Conclusion

This study demonstrates significant associations between contemporary GDMT—particularly ARNI therapy—and improvements in LVEF and device-detected arrhythmic

burden in ICD recipients. However, given the retrospective design and potential confounding factors, these findings should be considered hypothesis-generating rather than practice-changing. Prospective studies incorporating standardized device programming and time-dependent analyses are required to clarify the independent antiarrhythmic effects of these therapies.

Authors' contributions

All authors contributed to the writing and have approved the final version of the manuscript. Conceptualization: F.Ö, MY; Study Design: F.Ö, MY; Supervision: F.Ö, MY; Resources: F.Ö, MY; B.Y. Biological Sample/Data Provision: F.Ö, MY; Data Collection & Processing: F.Ö, MY; Data Analysis & Interpretation: F.Ö, MY; Literature Review: F.Ö, MY; Writing – Original Draft: F.Ö, MY; Writing – Review & Editing (Critical Revision): F.Ö, MY;

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Data availability

The datasets supporting the conclusions of this article are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This study followed the Declaration of Helsinki, and Zonguldak Bülent Ecevit University Ethics Committee approved the study (Approval Number: 2025/17, Date: 01 October 2025). As the study involved retrospective review of existing medical records, the requirement for written informed consent was waived by the ethics committee.

Competing interests

The authors declare no competing interests.

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not applicable.

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