

How Do Arrhythmia Markers Change on the ECG of Patients Using ARNI?

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ABSTRACT

The objective of this study was to examine the electrocardiographic changes in heart failure patients with low ejection fraction receiving sacubitril/valsartan(S/V).

The study comprised 234 patients diagnosed with heart failure and undergoing treatment between 2020 and 2025, whose files were retrospectively reviewed. The ECG findings were subjected to thorough analysis and meticulous recording.

An evaluation of the treatment characteristics revealed that all patients were receiving S/V therapy, with 73.5% of patients using SGLT2 inhibitors, 75.6% using beta-blockers, 66.7% using acetylsalicylic acid, 42.3% using P2Y12 inhibitors, 66.2% using diuretics, and 57.7% using spironolactone. Subsequent to S/V administration, a decline in the QT, QTc, QTd, Tp-e, and Tp-e/QTc values was observed on the ECG ($p<0.001$).

In the context of heart failure treatment, S/V therapy has been observed to effect positive changes in ECG findings and markers of arrhythmia

Keywords: heart failure, sacubitril/valsartan, ECG

Introduction

Heart failure (HF) is a significant cause of mortality, with a prevalence of 1-2% depending on age and a 5-year survival rate of only 40-50%. (1-3). The Sacubitril/Valsartan treatment, as evidenced by the findings of the PARADIGM-HF study, has been demonstrated to reduce the probability of sudden cardiac death, concurrently decreasing the number of hospital admissions. This treatment has emerged as a prevalent pharmaceutical agent in the management of heart failure.(4) Sacubitril/valsartan(S/V) is a combination of an angiotensin receptor blocker (ARB)(valsartan) and a neprilysin inhibitor (sacubitril). ARBs have been demonstrated to reduce vasoconstriction and aldosterone production whilst increasing natriuresis. Neprilysin, also known as an endopeptidase, is a zinc-dependent metalloprotease that inactivates several vasoactive peptides. (5) Neprilysin has been demonstrated to cleave natriuretic peptides, bradykinin, substance P, vasoactive intestinal peptide, glucagon, neurotensin, adrenomedullin, and amyloid- β . (6,7) It is hypothesized that the gradual inhibition of the neprilysin pathway may reduce the harmful effects of sympathetic nervous system activation. This, in turn, is predicted to

result in hemodynamic improvements and the reversal of left ventricular remodeling. (7,8) This intricate system suggests the possibility of beneficial effects on both ejection fraction (EF) and rhythm.

The available data on the effects of sacubitril/valsartan on arrhythmias in patients with heart failure are contradictory. De Diego et al. enrolled 120 patients suffering from heart failure with reduced ejection fraction (HFrEF) and implanted with a cardiac resynchronization therapy (CRT) device or an implantable cardioverter-defibrillator (ICD) who were prescribed angiotensin receptor–neprilysin inhibitors (ARNIs) as a substitute for angiotensin-converting enzyme inhibitors (ACEIs). The findings demonstrated that sacubitril/valsartan diminished the occurrence of sustained ventricular tachycardia (SVT), premature ventricular contractions (PVCs), and appropriate ICD shocks in patients with HF with HFrEF who underwent home monitoring, in comparison to the treatment of angiotensin inhibition. (9)

The addition of SGLT2 inhibitors to optimal medical treatment in patients with heart failure has been shown to positively alter various repolarisation markers (QT, QTc, QTd, Tp-e and

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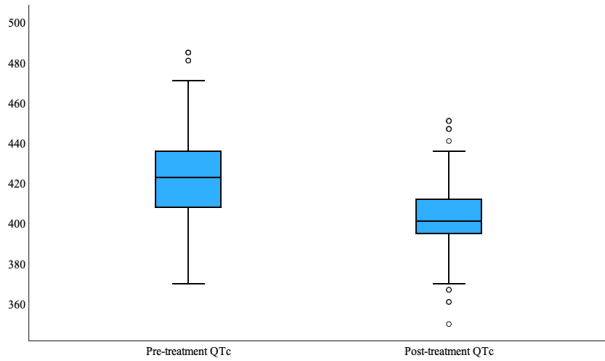


Fig. 1. Distribution of QTc values before and after treatment

Tp-e/QTc), thereby contributing to the hypothesis that SGLT2 inhibitors may have a positive effect on arrhythmias. (10) The precise mechanism by which SGLT2i exerts its effect remains to be elucidated. While the utilization of S/V has been demonstrated to yield a comparable favorable outcome to that of SGLT2i, there are ongoing studies that are investigating this topic. The objective of this study was to ascertain how S/V utilization affects the ECG.

Materials and Methods

The present study retrospectively included 234 patients diagnosed with heart failure who were receiving private Kdz Ereğli Echomar Hospital treatment between 2020 and 2025. Ethical approval for the study was obtained from the Zonguldak Bulent Ecevit University ethics committee. Patients who were pregnant, had known arrhythmias (e.g., atrial fibrillation (AF), ventricular tachycardia (VT), or ventricular fibrillation (VF)), renal failure, chronic liver disease, familial hyperlipidemia, or malignancy were excluded from the study.

All participants in the study underwent electrocardiography, their medications were reviewed, and physical examinations were performed. Echocardiography was performed on each individual to assess mechanical myocardial function. The echocardiographic examination was conducted following a minimum of 15 minutes of rest in the left lateral position (2-dimensional, M-mode, Doppler echocardiography) utilizing a Vivid E9 device with an X5-1 transthoracic probe via parasternal and apical windows. Echocardiography was performed on each participant according to the standard images and techniques outlined in the European Society of Echocardiography (AEC) guidelines.

The ECG results of patients under observation with KY were reported by a cardiologist specializing in this field, who was unaware of the patients' identities, and S/V was added to their treatment. Twelve months later, ECG parameters were reported once more by the same cardiologist. Participants received 12-lead ECG recordings (Nihonkohden brand) at room temperature (20°C–24°C) following a 30-minute period of rest. All ECGs were meticulously scanned, and in order to mitigate potential errors, the data were transferred to a personal computer and analyzed with Adobe Photoshop at 400% magnification. Individuals exhibiting a U-wave on their ECGs were excluded from the study. The mean value was calculated for each lead, with an average of three values being obtained for each. The QT interval was measured from the beginning of the QRS complex to the end of the T wave, and the corrected QT for heart rate was calculated using the Bazett formula ($QTc = QT\sqrt{(R-R \text{ interval})}$). The term "QT dispersion" (QTd) was defined as the difference between the maximum and minimum QT intervals in 12 leads. The Tp-e interval was defined as the interval from the peak of the T wave to the end of the T wave. The interval between the top and bottom was measured from the precordial leads. (11,12)

Patients with a QTc interval exceeding 500 msec were not initiated on QT-prolonging medication, if their QTc interval persisted beyond 500 msec while on such medication, their treatment was modified (if they were receiving multiple QT-prolonging medications, the dosage of one or more of these medications was reduced; if they were taking only one QT-prolonging medication, that medication was discontinued).

Statistical Analysis: Statistical analysis of the data obtained in the study was performed using IBM Statistical Package for the Social Sciences (SPSS) for macOS, version 30.0 (IBM Corp., Armonk, NY, USA). The distribution characteristics of continuous variables were evaluated using the Shapiro–Wilk test; skewness and kurtosis values were also considered using histogram graphs. Continuous variables were presented as mean $\pm$ standard deviation or median (interquartile range, IQR) according to their distribution characteristics, while categorical variables were presented as number and percentage [n (%)]. Since the distribution of differences between pre- and post-treatment electrocardiographic (ECG) parameters showed a normal distribution, paired Student t-tests were used for comparisons. Multivariate linear regression analyses were applied to evaluate the

factors affecting post-treatment QT, QTc, QTd, Tpe, and Tpe/QTc measurements; the model for QTc, the most clinically significant parameter, is presented in the main article, and the results of other analyses are summarized in the text. In regression analyses, age and gender were included as principal covariates along with the pre-treatment measurement of the relevant ECG parameter. Model fit was evaluated using the coefficient of determination (R^2), adjusted R^2 , and F-test. Multicollinearity was examined using variance inflation factor (VIF) values. Results were presented as regression coefficient (B), standard error, and p-value. In all statistical analyses, a two-sided $p < 0.05$ value was considered statistically significant.

Results

Please refer to Table 1 for details of the patients' demographics and clinical characteristics. The study comprised a total of 234 patients. The demographic composition of the patient population was as follows: 53.8% of patients were male, while 46.2% were female, with an average age of 62 years (± 14 years). The prevalence of smoking was documented in 28.2% of the patient population. A subsequent evaluation of comorbidities revealed that 46.2% of patients had been diagnosed with coronary artery disease, 53% with hypertension, and 38.5% with diabetes mellitus.

Treatment characteristics were evaluated, revealing that all patients were receiving S/V therapy, with 73.5% using SGLT2 inhibitors, 75.6% using beta-blockers, 66.7% using acetylsalicylic acid, 42.3% using P2Y12 inhibitors, 66.2% using diuretics, and 57.7% using spironolactone.

The distribution of electrocardiographic findings before and after treatment is shown in Table 2. QT duration was significantly reduced after treatment ($p < 0.001$). Similarly, QTc duration was also significantly shortened after treatment ($p < 0.001$). QT dispersion was significantly reduced after treatment ($p < 0.001$), and Tpe duration was also significantly reduced ($p < 0.001$). Furthermore, a significant decrease in the Tpe/QTc ratio was observed after treatment ($p < 0.001$).

Multivariate linear regression analysis was employed to analyze the factors affecting patients' post-treatment QT interval measurements, and the results indicated that these factors were statistically significant ($F = 7.924$; $p < 0.001$). The analysis explained approximately 23% of the variance in post-treatment QT interval (adjusted $R^2 = 0.229$). Patients' baseline QT value (preQT)

was identified as the strongest predictor of post-treatment QT interval ($B = 0.458$; $p < 0.001$). Consequently, an increase of 1 ms in the baseline QT interval was found to correspond to a mean increase of approximately 0.46 ms in the post-treatment QT interval. With regard to the utilization of pharmaceuticals, no independent effect of SGLT2 inhibitors, beta-blockers, NOACs, ASA, P2Y12 inhibitors, diuretics, and spironolactone on the QT interval was identified ($p > 0.05$). Furthermore, the investigation revealed that neither age nor gender exhibited a significant correlation with post-treatment QT interval.

The factors affecting post-treatment QTc measurement in patients are presented in Table 3. The established multivariate model is statistically significant ($F = 14.635$; $p < 0.001$) and explains 36.9% of the variance in QTc duration (adjusted $R^2 = 0.369$). Patients' baseline QTc value was identified as the strongest predictor of post-treatment QTc duration ($B = 0.473$; $p < 0.001$). In the course of the evaluation of medications, there was an independent and statistically significant association between SGLT2 inhibitor use and an increase in post-treatment QTc duration ($B = 5.07$ ms; $p = 0.036$). The utilization of beta-blockers exhibited a propensity for an increase in QTc duration; nevertheless, this correlation failed to attain statistical significance ($p = 0.085$). The investigation revealed no substantial correlation between QTc duration and other pharmaceutical categories, including NOACs, ASA, P2Y12 inhibitors, diuretics, and spironolactone. Furthermore, the investigation revealed that neither age nor gender were found to be independent predictors of QTc.

The factors that affect patients' post-treatment QTd measurement are as follows: The regression model was not found to be statistically significant ($F = 0.370$; $p = 0.958$), and the explained variance was quite low (adjusted $R^2 = -0.028$). No significant relationship was found between patients' baseline QTd value and post-treatment QTd ($p = 0.773$). Furthermore, the evaluation of the drugs revealed that none of them demonstrated an independent effect on QTd ($p > 0.05$). Furthermore, the investigation revealed that neither age nor gender exhibited a significant correlation with QTd duration.

The following factors have been identified as affecting TPE measurement after treatment in patients:

- The established regression model is statistically significant ($F = 1.946$; $p = 0.040$).

Table 1: Distribution of Demographic and Clinical Findings of Patients

Variables (N=234)	n (%)	Mean $\pm$ SD	Median (IQR)
Sex			
Male	126 (53,8)		
Female	108 (46,2)		
Age (year)		62 $\pm$ 14	61 (53-71)
Smoking	66 (28,2)		
Additional illnesses			
CAD	108 (46,2)		
HT	124 (53)		
DM	90 (38,5)		
Laboratory			
LDL		117,2 $\pm$ 36,9	118 (96-142)
Cholesterol		160,7 $\pm$ 42,5	160 (116-197)
Triglycerides		284,6 $\pm$ 61,7	282,5 (254-342)
VLDL		47,7 $\pm$ 21,1	51 (28-62)
Uric acid		9 $\pm$ 2,7	9,9 (6,5-11,4)
Glucose		126 $\pm$ 55	106,5 (91-139)
ALT		38,5 $\pm$ 74,6	23 (15,3-39)
AST		43 $\pm$ 60,6	28,7 (19-40)
Creatinine		1,1 $\pm$ 0,7	0,9 (0,8-1,2)
Potassium		4,4 $\pm$ 0,7	4,3 (4-4,7)
Sodium		139,4 $\pm$ 4,1	139 (137-142)
Hemoglobin		13,7 $\pm$ 1,7	13,6 (12,7-14,9)
EF(%)		36,3 $\pm$ 11,9	38 (25-45)
Treatments			
S/V	234 (100)		
SGLT2i	172 (73,5)		
BBLOC	177 (75,6)		
NOAK	69 (29,5)		
ASA	156 (66,7)		
P2Y12	99 (42,3)		
Diuretic (furosemide)	155 (66,2)		
Spirolactone	135 (57,7)		

CAD: coronary artery disease, HT: hypertension, DM: Diabetes mellitus, LDL: Low-density lipoprotein, VLDL: Very-low-density lipoprotein, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, EF: Ejection fraction, S/V: sacubitril/valsartan, SGLT2i: sodium-glucose cotransporter-2 inhibitors, BBLOC: Beta blocker, NOAC: Non-Vitamin K Antagonist Oral Anticoagulant, ASA: Acetylsalicylic acid,

- However, the explained variance is low (adjusted $R^2=0.039$). Patients' baseline TPE value was identified as an independent predictor of post-treatment TPE duration ($B=0.246$; $p<0.001$). When the relationship between drug use and TPE duration was evaluated, no significant relationship was observed ($p>0.05$). This observation was made when SGLT2 inhibitors, beta-blockers, NOACs, ASA, P2Y12 inhibitors, diuretics, and spironolactone were considered.

The findings revealed that neither age nor gender exhibited an independent effect on TPE duration. The present study examined the factors that affect the TPE/QTc ratio of patients following treatment. The established regression model was not statistically significant ($F=0.678$; $p=0.744$), and the explained variance was quite low (adjusted $R^2=-0.014$). The baseline TPE/QTc ratio of patients was found to be a significant predictor of post-treatment TPE/QTc ($B=0.148$; $p=0.035$). The investigation revealed no evidence of an

Table 2: Distribution of Patients' Pre- and Post-Treatment ECG Findings

ECG findings	Before treatment	After treatment	p-value
	Mean $\pm$ SD	Mean $\pm$ SD	
QT	398,3 $\pm$ 29,5	369,9 $\pm$ 26,7	<0,001
QTc	423,7 $\pm$ 21,1	403,1 $\pm$ 16,7	<0,001
QTd	52 $\pm$ 1,5	47,9 $\pm$ 1,8	<0,001
Tpe	81,4 $\pm$ 9,3	71,4 $\pm$ 9,5	<0,001
Tpe/QTc	0,190 $\pm$ 0,021	0,176 $\pm$ 0,022	<0,001

Data are presented as mean $\pm$ standard deviation. p-values were obtained using a paired Student t-test

Table 3: Factors Affecting QTc Measurement After Treatment In Patients

Variable	B	Standard error	t	p-value
Age(year)	-0,060	0,066	-0,917	0,360
Sex (Male=1, Female=2)	-0,420	1,768	-0,238	0,812
SGLT2i	5,070	2,404	2,109	0,036
BBLOC	6,574	3,803	1,729	0,085
NOAK	1,595	2,733	0,584	0,560
ASA	-1,144	3,779	-0,303	0,762
P2Y12	-1,098	1,826	-0,601	0,548
Diuretic (furosemide)	-2,539	1,941	-1,309	0,192
Spironolactone	-3,046	1,997	-1,526	0,129

Model Summary: R=0.629; R²=0.396; Adjusted R²=0.369; F=14.635; p<0.001

SGLT2i: sodium-glucose cotransporter-2 inhibitors, BBLOC: beta-blocker, NOAC: Non-Vitamin K Antagonist Oral Anticoagulant, ASA: Acetylsalicylic acid,

independent relationship between medication use, age, and gender, and the TPE/QTc ratio.

Discussion

The natural progression of heart failure with reduced ejection fraction is typified by the occurrence of progressive and harmful structural remodeling (13,14). Cardiac remodeling and fibrosis have become recognized as significant risk factors for malignant ventricular arrhythmias (13,14). Cardiac remodeling and fibrosis have become recognized as significant risk factors for malignant ventricular arrhythmias. (15) The present study included patients diagnosed with low ejection fraction heart failure, with an average EF value of 36.3 $\pm$ 11.9%. These patients were deemed to be at risk of developing arrhythmias. In order to address the question of how S/V use affects arrhythmia markers on the ECG, an examination of the ECG findings of these patients was conducted.

A study of 151 patients suffering from heart failure and switching from ACE inhibitors or ARBs to sacubitril/valsartan revealed that the initiation of sacubitril/valsartan was associated

with a reduced incidence of ventricular arrhythmias and fewer ICD interventions. In addition, a statistically significant reduction in PVCs and an improvement in BiV pacing were also observed. (16) In a prospective observational study of 167 patients diagnosed with dilated cardiomyopathy and reduced ejection fraction who had dual-chamber ICDs, sacubitril/valsartan was found to reduce the incidence of atrial and ventricular arrhythmias. (17) However, contradictory findings have been reported in certain studies. A subanalysis of 108 patients from the SUMA study revealed that six patients (5.6%) experienced arrhythmic storms following the initiation of sacubitril/valsartan treatment, while in five patients, VA was no longer observed after sacubitril/valsartan was discontinued. (18)

A review of the extant literature reveals that numerous studies have demonstrated a correlation between ventricular repolarization defects and the occurrence of fatal arrhythmias, as well as an association with sudden cardiac death. (19,20) Electrocardiographic studies demonstrate that the Tp-e interval can be utilized as an indicator of transmural, global repolarization distribution, and an increased Tp-e interval has been demonstrated

to be associated with increased susceptibility to ventricular tachyarrhythmia and cardiovascular mortality in patients. (21,22) QT and QTc intervals are well-known and widely utilized parameters of myocardial repolarisation. They have been demonstrated to be associated with ventricular arrhythmias and cardiovascular mortality. (23) Conversely, an increase in QTd value has been demonstrated to result in an elevated risk of ventricular arrhythmias. (24) It is suggested that the Tp-e/QT ratio is a more specific and accurate measure of the distribution of ventricular repolarization than the QT and Tp-e intervals. (25)

The Tp-e/QTc ratio is regarded as a novel index for arrhythmia occurrence and can more accurately assess the distribution of ventricular repolarization when compared to the use of Tp-e or QTc intervals alone. (25) The present study investigates the impact of S/V therapy on arrhythmia markers on ECG in patients diagnosed with heart failure, examining ECG findings one year after the initiation of S/V therapy in patients receiving heart failure treatment. A significant decrease in QT, QTc, QTd, Tpe, and Tpe/QTc intervals was observed in the post-treatment period ($p < 0.001$). This finding serves to reinforce the hypothesis that S/V therapy may reduce the likelihood of arrhythmias. Nevertheless, the precise mechanism by which S/V therapy reduces ventricular arrhythmias remains to be elucidated. The antiarrhythmic effect has been associated with various potential mechanisms. The underlying mechanisms through which this reduction occurs remain to be elucidated. Potential explanations include reduced remodeling, decreased cardiac fibrosis, wall stretching, sympathetic nervous system activation, or alternatively, electrical remodeling. (26-28) Despite the ambiguity surrounding the impact of S/V on arrhythmia, it is hypothesized that it may attenuate rhythm disturbances by virtue of its diminished remodeling and its contribution to EF. However, further comprehensive studies are required to substantiate this hypothesis.

The antiarrhythmic effect of S/V use becomes more pronounced over time, as evidenced by a review of the literature, which demonstrates that its effect is more evident after six months and beyond. (9,29,30) The present study also examined the findings after 12 months and obtained results consistent with those of the aforementioned studies.

In a separate study on S/V-related heart failure patients, the opposite was observed: namely, a

prolongation of the QT interval. This was interpreted as being due to reduced remodeling, and it was suggested that QT prolongation would be related to the patient's effective medication use and would similarly contribute to the patient's EF level. (31) Although QT prolongation was observed in a number of patients in the present study, this was not statistically significant.

Numerous studies have demonstrated that SGLT2, another pharmaceutical agent employed in the treatment of heart failure, exerts a favorable effect on the ECG. Sodium-glucose cotransporter-2 (SGLT-2) is predominantly expressed in the kidneys and is responsible for the reabsorption of sodium (Na^+) and glucose in the renal tubules. (32) The inhibition of SGLT-2 has been demonstrated to increase urinary glucose excretion and improve natriuresis in patients diagnosed with type 2 diabetes mellitus. (33) Subsequent studies demonstrated the efficacy of this property in the treatment of diabetes mellitus, and its use in heart failure treatment was initiated as a result of its positive effects on heart failure patients. It has been hypothesized that SGLT-2 inhibitors achieve this by reducing cardiac preload. (34,35) In patients suffering from heart failure and exhibiting low EF, the incorporation of SGLT2 inhibitors into optimal medical treatment regimens has been demonstrated to engender favorable alterations in ECG parameters, including QT, QTc, QTd, Tp-e and Tp-e/QTc. (10,36) Although the study observed a statistically significant reduction in QTc values, its effect on other ECG changes was not as significant as that of S/V. This may be attributable to the fact that our investigation commenced with S/V in patients who were already using SGLT2i and receiving heart failure treatment. It can be hypothesized that had these patients been observed prior to the administration of SGLT2i and subsequently re-evaluated following treatment, it is possible that more substantial outcomes may have been observed. Given that the patient group examined may have already experienced a positive effect from SGLT2i, it can be concluded that a positive effect was created, even though no significant results were observed in this study. However, the extant literature also contains studies which demonstrate that the effect of SGLT2i use on ECG is limited. For example, Wu VC-C et al. compared type 2 diabetic patients using and not using SGLT2 inhibitors, showing no difference in PR interval, QT interval, ST-T changes, bundle branch block, or ventricular arrhythmias in patients using SGLT2 inhibitors. (37) Furthermore, it was highly

probable that the combination of beta-blockers and SGLT2 inhibitors in patients may have already demonstrated positive effects on the ECG.

In conclusion, the present study has demonstrated that the administration of sacubitril/valsartan to patients diagnosed with low ejection fraction heart failure results in a reduction in ECG parameters that are utilized for the prediction of arrhythmias, including QT, QTc, QTd, Tp-e and Tp-e/QTc. Moreover, it would be more precise to state that this application may reduce the incidence of arrhythmias in these patients in long-term follow-ups. As is known, the technology can be used in the prediction of arrhythmia using ECG parameters, and the findings of this study suggest that its effect on these parameters is positive. It is evident that, given the considerable number of patients included in the present study and the numerous factors that influence its findings, further development and more comprehensive studies are required.

Study limitations: The present study is retrospective in nature, which precludes the clear examination of the progressive development of patients. The number of patients is relatively small; more comprehensive randomized studies are required. It is evident that the limited number of patients and the absence of diversity in the patient population preclude the ability to provide a meaningful commentary on the interaction of S/V with other pharmaceutical agents. Further studies are requisite to address this knowledge gap. The arrhythmia effect of S/V remains unexplained; further research in laboratory settings is required to elucidate this phenomenon.

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