ORIGINAL RESEARCH

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The Positive Effect of Sacubitril-Valsartan Treatment on Frontal QRS-T Angle in Patients with Heart Failure

Kalp Yetmezliği Olan Hastalarda Sakubitril-Valsartan Tedavisinin Frontal QRS-T Açısı Üzerine Olumlu Etkisi

Mehmet Karaca[1], Evliya Akdeniz[2]

[1]Üsküdar University, Ataşehir Memorial Hospital, Department of Cardiology, İstanbul, Turkey
[2]University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Department of Cardiology, İstanbul, Turkey

Abstract

Objective: Introducing angiotensin receptor neprilysin inhibitors (ARNI) to daily clinical practice is one of the most important advances in the treatment of heart failure (HF). ARNI is associated with reduced mortality and hospitalization in HF patients due to structural and electrical remodelling. In this study, we investigated the effect of sacubitril/valsartan on the frontal QRS-T angle (f-QRS/Ta), which reflects abnormal ventricular repolarization, in patients with HF with reduced ejection fraction (HFrEF).

Method: The difference of f-QRS/Ta obtained from surface electrocardiograms (ECG) in patients with HF and systolic disfunction (EF ≤40%) before and after initiating ARNI treatment was evaluated retrospectively. Demographic, clinic and ECG characteristics of patients collected from hospital data and compared at one year follow-up.

Results: A total of 45 patients were enrolled in this study of whom 15 were female (33.3%). The mean NYHA class of the study population was class 2, and the mean left ventricle EF was 30%. ARNI treatment significantly reduced the QRS duration and f-QRS/Ta compared to the baseline ECG parameters. The mean QRS duration decreased from 106.9±10.3 msto 105±9.8 ms at 12 months follow-up, while the baseline f-QRS/Ta of 72.3±12° reduced to 67.4±12.6° after treatment and respectively p-values 0.008 and<0.001 were detected.

Conclusion: Our study has shown that in HFrEF patients, sacubitril/valsartan treatment led to a significant decrease in QRS duration and f-QRS/Ta values.

Keywords: ARNI, frontal QRS/Ta, heart failure

Öz

Amaç: Anjiyotensin reseptör neprisilin inhibitörlerinin (ARNI) günlük klinik uygulamaya dahil edilmesi, kalp yetmezliği (KY) tedavisinde yapısal ve elektriksel yeniden şekillenme yoluyla mortaliteyi ve hastaneye yatışları azaltması nedeniyle en önemli gelişmelerden biridir. Bu çalışmada, sacubitril/valsartanın azalmış ejeksiyon fraksiyonlu KY (HFrEF) olan hastalarda anormal ventriküler repolarizasyonu yansıtan frontal QRS-T açısı (f-QRS/Ta) üzerindeki etkisi araştırıldı.

Yöntem: Azalmış ejeksiyon fraksiyonlu KY olan hastalarda yüzey elektrokardiyogramlarından (EKG) elde edilen f-QRS/Ta farkı, ARNI tedavisinin başlatılmasından önce ve sonra retrospektif olarak değerlendirildi. Demografik, klinik ve EKG özellikler hastane verilerinden toplandı ve bir yıllık takipte karşılaştırıldı.

Bulgular: Çalışmaya toplam 45 hasta dahil edildi ve bunların 15'i kadın (%33,3) idi. Çalışma popülasyonunun ortalama NYHA sınıfı 2, sol ventrikül ejeksiyon fraksiyonu (EF) ise %30'du. ARNI tedavisi, QRS süresi ve f-QRS/Ta değerlerinde başlangıç EKG parametrelere kıyasla anlamlı bir azalmaya neden oldu. Ortalama QRS süresi, başlangıçta 106,9±10,3 ms'den 12 aylık takipte 105±9,8 ms'ye düştü. Başlangıç f-QRS/Ta değeri ise 72,3±12° iken tedavi sonrası 67,4±12,6°'ye düştü ve sırasıyla p-değerleri 0,008 ve <0,001 olarak tespit edildi.

Sonuç: Çalışmamız, HFrEF hastalarında sacubitril/valsartan tedavisinin QRS süresi ve f-QRS/Ta değerlerinde anlamlı bir azalmaya yol açtığını göstermiştir.

Anahtar kelimeler: ARNI, kalp yetmezliği, frontal QRS/Ta

Address for Correspondence: Mehmet Karaca, Üsküdar University, Ataşehir Memorial Hospital, Department of Cardiology, İstanbul, Turkey
E-mail: mehmetkaraca06@gmail.com **ORCID:** orcid.org/0000-0001-8771-0539
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Introduction

Heart failure (HF) is a complex clinical syndrome that affects more than 64 million people worldwide (1). Long-term mortality rate remains over 50% despite contemporary advancements in treatment. In recent years, one of the most significant developments in HF treatment has been the demonstration of the favorable effects of angiotensin receptor neprilysin inhibitors (ARNI) on mortality and hospitalization (1,2). Therefore, in the current HF treatment guidelines of the European Society of Cardiology, ARNI is recommended as a first line treatmentoption (3). Sacubitril/valsartan (Sac/Val) is thecurrent ARNI used in HF treatment which consists valsartan, an angiotensin receptor blocker, and sacubitril, a molecule that inhibits the enzyme neprilysin, responsible for the degradation of endogenous vasoactive peptides like natriuretic peptides and bradykinin. In the prospective comparison of ARNI with angiotensin-converting enzyme inhibitor to determine impact on global mortality and morbidity in HF trial (PARADIGM-HF) study, it was observed that Sac/Val significantly reduced all-cause mortality, HF-related hospitalizations and cardiovascular mortality rates compared to enalapril. These results highlight the superiority of Sac/Val over traditional ACE inhibitors in improving outcomes in HF patients (2). The positive effect of Sac/Val on HF is classically attributed to the blockade of the renin-angiotensin-aldosterone system (RAAS) and the inhibition of natriuretic peptide breakdown, resulting in a reduction of myocyte injury, inflammation and fibrosis (4).

Electrocardiographic (ECG) changes are quite commonly encountered in patients with HF. These changes include conduction abnormalities, T-wave abnormalities, prolongation of QRS duration and QT interval, pathological Q waves, atrial fibrillation, and changes in the QRS-T angle (5,6). There is a significant association between a wide QRS-T angle, which is one of the markers of abnormal ventricular repolarization, and HF. It has been shown that a wide QRS-T angle increases the risk of developing HF by approximately threefold (7). Additionally, there is a significant association between a wide QRS-T angle and mortality. A wider QRS-T angle has also been linked to an increased risk of mortality in patients, particularly in those with HF (7,8).

Beyond its neurohormonal properities, the Sac/Val combination has also been observed to have electrophysiological effects, such as reduction in heart rate, QRS duration, and QTc interval as demonstrated in various studies. These electrophysiological effects may contribute to the overall improvement in ventricular function in HF patients (9,10). In this study, the effect of Sac/Val treatment on thefrontal QRS-T angle (f-QRS/Ta) changeswhichare known to be related with unfavourable eventsin patients HF with reduced ejection fraction (HFrEF) at long term follow-up was investigated.

Materials and Methods

Study Population

This study was designed retrospectively to evaluate patients with HF and a left ventricular ejection fraction (LVEF) ≤40% who were treated with ARNI and admitted to our cardiology outpatient clinic between January 2021 and February 2022. Patients with HFrEF older than 18 years and in New York Heart Association (NYHA) functional class 1-3, who were receiving guideline-directed medical therapy, were included in the study. Patients with NYHA functional class 4, chronic renal failure (GFR<60 mL/min/1.73 m²), atrial fibrillation, permanent pacemaker, left or right bundle branch block, or end-stage oncology were excluded from the study. Additionally, those unable to tolerate ARNI treatment or with difficulties in interpreting ECG were also excluded. The study was conducted in accordance with the ethical rules stated in the Declaration of Helsinki and the study protocols were approved by the Memorial Ataşehir Hospital Ethics Committee (decision no: 2024/15 date: 16.01.2025). Informed consent for this study was waived as it was a retrospective analysis. Informed consent for this study was waived because it was a retrospective analysis.

Data Collection

The baseline characteristics and laboratory data of all patients were obtained through retrospective screening of the hospital information system. The 12-lead surface ECGs were taken in the supine position at a paper speed of 25 mm/s, and recordings were obtained from patient files and were independently evaluated by two different cardiologists blinded to patients' data. All ECG records were scanned into electronic format using Adobe Photoshop (Adobe Inc., San Jose, CA, USA) and magnified by 400% to reduce errors. The P wave duration, PR interval, QRS duration, and QT duration on the ECG were measured using a digital millisecond timer. QTc was obtained by correction of QT duration for heart rate using the Bazett's formula (11). The f-QRS/Ta was determined as the absolute difference between the frontal QRS and T-wave axes, which were automatically derived from the ECG machine [Schiller, Cardiovit AT-102 G2 Switzerland)] as demonstrated in

Figure 1. The f-QRS/Ta values greater than 180° were subtracted from 360°. LVEF obtained by modified Simpson method using a Philips EPIQ 7 device (Philips Healthcare, Andover, USA) and a 2.5 MHz probe.

Statistical Analysis

Categorical data were expressed as frequencies and percentages and analyzed with Pearson's chi-square test, while continuous data were presented as mean ± standard deviation and analyzed with the Student's t-test. The Kolmogorov-Smirnov test was employed for variables with normal distribution. NT-proBNP levels, New York Heart Association functional class, and ECG indices (heart rate, QRS complex, QTc interval, T wave angle, QRS angle, f-QRS/Ta) were recorded both before and after ARNI treatment. A p-value of less than 0.05 was considered statistically significant. Statistical analyses and calculations were carried out using SPSS software, version 22.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 63 patients with HFrEF who presented to the cardiologyoutpatient clinic were initially considered for the study. Following the application of the exclusion criteria, 18 patients were excluded, and 45 patients wererecruited in thisstudy. 71.1% of the patients (n=32) had an ischemic etiology. The mean NYHA class of the study population wasclass 2 and the meanleftventricle ejection fraction was 30%. The maximum tolerable ARNI doses for the patients were as follows: 8 patients (17.8%) received 100 mg/day, 16 patients (35.6%) received 200 mg/day, and 21 patients (46.7%) received 400 mg/day. Baseline characteristics, clinical, laboratory and echocardiographic variables are listed in Table 1.

After 12 months of treatment with the maximum tolerable dose of ARNI, the ECG parameters were reassessed during the follow-up visit. Significant reduction was observed in the QRS duration and f-QRS/Ta compared to the ECG parameters obtained at the beginning of the treatment.

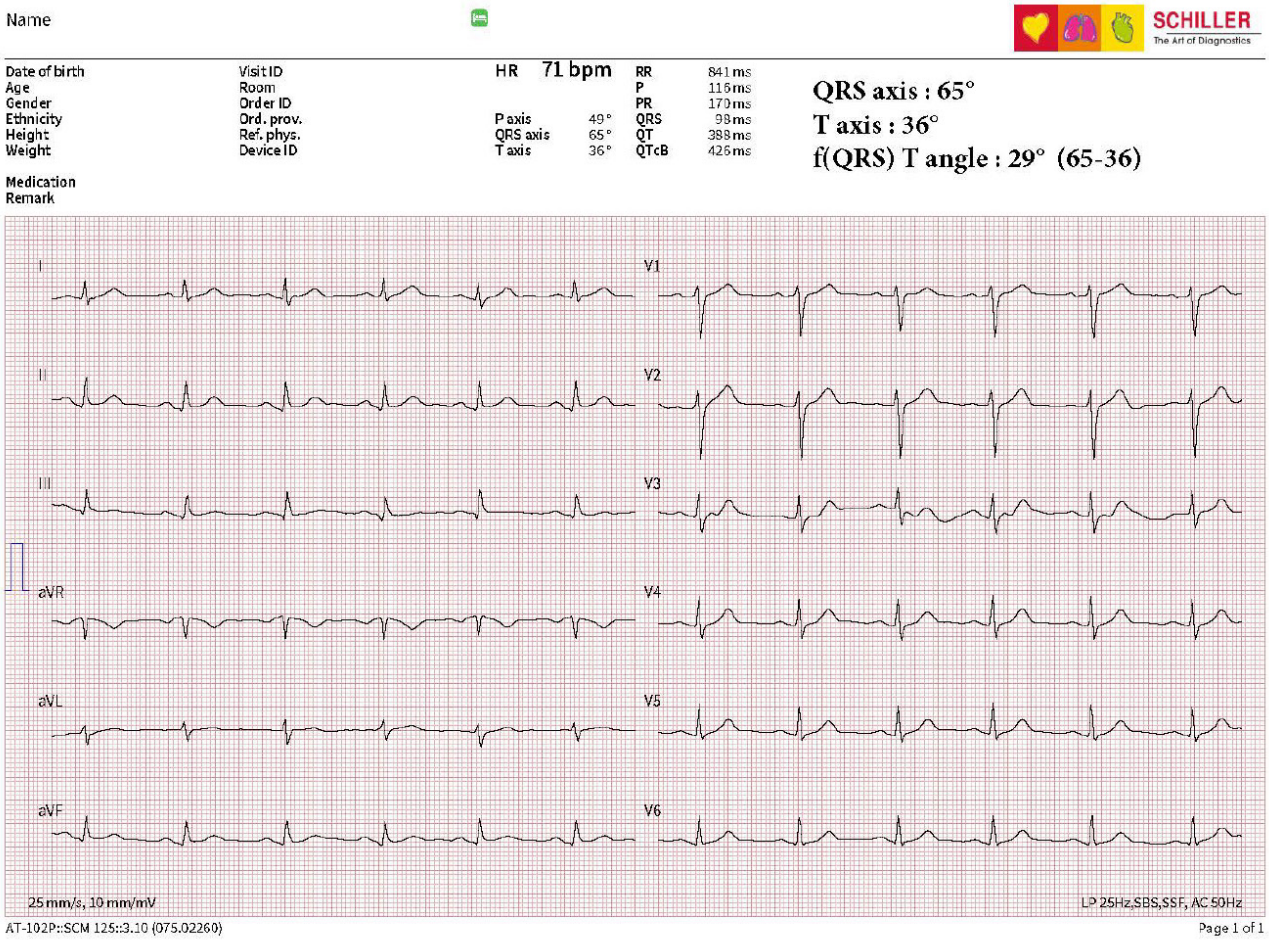

Figure 1. Example of f(QRS-T) angle calculation

The mean QRS duration decreased from 106.9±10.3 milliseconds to 105±9.8 milliseconds (p=0.008). Similarly, the baseline f-QRS/Ta of 72.3±12° was reduced to 67.4±12.6° after treatment, with p-values <0.001. Changes in ECG parameters observed during the treatment process are shown in Table 2.

Table 1. Demographic, clinical, laboratory and echocardiographic features

Variables	(n=45)
Demographic parameters	
Age, years	56.64±5.04
BMI, kg/m²	27.70±1.01
Female, n (%)	15 (33.3)
Hypertension, n (%)	16 (35.6)
Diabetes mellitus, n (%)	14 (34.1)
Smoking, n (%)	15 (33.3)
COPD, n (%)	9 (20)
Dyslipidemia, n (%)	13 (28.9)
Cerebrovascular disease, n (%)	4 (8.9)
Ischeamic etiology, n (%)	32 (71.1)
NHYA functional class	2.00±0.71
Laboratory parameters	
CRP mg/dL	4.04±2.03
Uric aside mg/dL	4.96±1.83
Albumin g/L	35.36±3.01
Sodium mEq/L	137.78±4.13
Potassium mEq/L	3.88±0.36
Haemoglobin g/dL	12.64±1.21
Glucose mg/dL	102.62±36.70
Glomerular filtration rate mL/dk/1.73 m²	85.20±8.19
Medications	
Beta-blocker therapy, n (%)	38 (84.4)
Thiazide diuretics, n (%)	14 (31.1)
Mineralocorticoid receptor antagonists, n (%)	33 (73.3)
Ivabradine, n (%)	12 (26.7)
Digoxin, n (%)	7 (15.6)
ARNI 100 mg, n (%)	8 (17.8)
ARNI 200 mg, n (%)	16 (35.6)
ARNI 400 mg, n (%)	21 (46.7)
Furosemide mg	33.29±10.23
Echocardiographic parameters	
LVH, n (%)	6 (13.3)
Severe mitral regurgitation, n (%)	3 (6.7)
Severe tricuspid regurgitation, n (%)	4 (8.9)
Severe aortic stenosis, n (%)	1 (2.2)
Atrial dilatation, n (%)	7 (15.6)
RV dysfunction, n (%)	7 (15.6)
LV ejection fraction %	30.26±3.91

ARNI: Angiotensin receptor neprilysin inhibitors, BMI: Body mass index, COPD: Chronic obstructive pulmonary disease, CRP: C-reactive protein, LV: Left ventricule, LVH: Left ventricular hypertrophy, RV: Right ventricule

Discussion

The main finding of our study was the significant decrease in the QRS duration and f-QRS/Ta compared to baseline ECG after treatment with ARNI in patients with HFrEF on long-term follow-up.

HF is a major public health concern with a long-term mortality rate exceeding 50% (1). Therefore, knowing the predictors of mortality and identifying high-risk patient groups are crucial for the management of HF. The f-QRS/Ta is a parameter that can be easily obtained from a standard ECG and represents an approximate value of the spatial angles of ventricular depolarization and repolarization. An increase in the angle indicates a greater heterogeneity of ventricular depolarization and repolarization. There is a significant relationship between the f-QRS/Ta and mortality in patients with HF. Scientific evidence indicates that a wide f-QRS/T has been identified to be a predictor of mortality in these patients (5,8,12).

The relationship between repolarization heterogeneity and malignant ventricular arrhythmia has been shown in human *in vivo* studies (13,14). Moreover, Ilkhanoff et al. (15) demonstratedthatthere is a significant association between interstitial fibrosis detected by cardiac magnetic resonance and an abnormal QRS/T angle (odds ratio 3.05, 95% confidence interval, 1.69-5.48). In our study, the reduction observed in the f-QRS/Ta with Sac/Val therapy may have been a result of the reverse remodeling effect of ARNI treatment, as demonstrated in prospective study of biomarkers, symptom improvement, and ventricular remodeling during Sac/Val therapy for HF (PROVE-HF) study (16). The reduction in fibrosis burden due to reverse remodeling, along with the decrease in repolarization

Table 2. Comparison of ECG parameters and NT-proBNP

Parameters	Before therapy	Follow-up	p-value
NT-proBNP, pg/mL	2765.29±1035.15	2652.33±1334.45	0.551
Heart rate, bpm	70.82±10.4	68.69±9.38	**0.011**
QRS, msn	106.96±10.37	105.09±9.81	**0.008**
QTc	379.47±25.72	382.71±20.58	0.173
QRS-angle	58.64±37.11	58.00±30.35	0.614
T-angle	-13.47±40.71	-7.78±34.07	**0.020**
f-QRS/T angle	72.33±12.09	67.44±12.67	**<0.001**

BNP: Brain natriuretic peptide, ECG: Electrocardiogram

heterogeneity, is consistent with the reduction in the f-QRS/Ta. In a rabbit model of ischemic HF, it has been shown that ARNI treatment can reduce ventricular arrhythmias due to its effects on negative electrical and structural remodeling, as well as its anti-inflammatory properties (17). Additionally, the QRS/T angle is an important parameter that can be used not only in patients with HF but also for various clinical conditions such as acute myocarditis, myocardial infarction, or acute pulmonary embolism (18-21).

There are compelling evidences about relationship between the duration of the QRS complex and HF. The Framingham heart study has shown that, in patients without a history of HF, a prolonged QRS duration increases the risk of developing HF. Left ventricular intraventricular conduction delay, which is consequently prolonged QRS duration, are associated with more advanced myocardial damage and poorer prognosis compared to a narrow QRS complex (22,23). Studies on the effect of Sac/Val treatment on QRS duration in HF patients have shown that after Sac/Val therapy, there is a reduction in QRS duration, a decline in left ventricular systolic and diastolic diameters, improvement in ejection fraction, and enhancement in global longitudinal strain, reflecting improvements electrophysiological and mechanical parameters (24,25). These results, which can primarily be explained by reverse cardiac remodeling, are consistent with the improvements observed in left ventricular mechanical parameters in the PROVE-HF study (16). The results of our study also show a statistically significant reduction in QRS duration, compared to baseline after treatment in HF patients treated with ARNI, which is consistent with this scientific evidence.

Study Limitations

Our study had several limitations. Firstly, a relatively significant limitation was the small sample size of the study. Secondly, our study was designed as a retrospective study. Thirdly, our study was a single-center study. Finally, we had ECG records both before ARNI treatment and after one year of the follow-up period and were not able to evaluate the temporal changes of f-QRS/Ta values. Due to these restrictions, our study may need to be validated with comprehensive studies.

Conclusion

In conclusion, our study has shown that in HFrEF patients, Sac/Val treatment led to a significant decrease in QRS duration and f-QRS/Ta values. This effect suggests that Sac/Val treatment may have a significant role in the favorable clinical outcomes of HFrEF through its impact on electrical and structural remodeling.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the ethical rules stated in the Declaration of Helsinki and the study protocols were approved by the Memorial Ataşehir Hospital Ethics Committee (decision no: 2024/15 date: 16.01.2025).

Informed Consent: Informed consent for this study was waived because it was a retrospective analysis.

Footnotes

Authorship Contributions

Concept: M.K., Design: M.K., E.A., Data Collection or Processing: M.K., Analysis or Interpretation: M.K., E.A., Literature Search: M.K., E.A., Writing: M.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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References

1. Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GMC, Coats AJS. Global burden of heart failure: a comprehensive and updated review of epidemiology. Cardiovasc Res. 2023;119(6):1453.
2. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz M.P, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371(11):993-1004.
3. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42(36):3599-3726. Erratum in: Eur Heart J. 2021;42(48):4901.
4. Pascual-Figal D, Bayés-Genis A, Beltrán-Troncoso P, Caravaca-Pérez P, Conde-Martel A, Crespo-Leiro MG, et al. Sacubitril-valsartan, clinical benefits and related mechanisms of action in heart failure with reduced ejection fraction. A review. Front Cardiovasc Med. 2021;8:754499.
5. Sweda R, Sabti Z, Strebel I, Kozhuharov N, Wussler D, Shrestha S, et al. Diagnostic and prognostic values of the QRS-T angle in patients with suspected acute decompensated heart failure. ESC Heart Fail. 2020;7(4):1817-1829.
6. Khan NK, Goode KM, Cleland JG, Rigby AS, Freemantle N, Eastaugh J, et al. Prevalence of ECG abnormalities in an international survey of patients with suspected or confirmed heart failure at death or discharge. Eur J Heart Fail. 2007;9(5):491-501.
7. Rautaharju PM, Kooperberg C, Larson JC, LaCroix A. Electrocardiographic predictors of incident congestive heart failure and all-cause mortality in postmenopausal women: the Women's Health Initiative. Circulation. 2006;113(4):481-489.

8. Gotsman I, Shauer A, Elizur Y, Zwas DR, Lotan C, Keren A. Temporal changes in electrocardiographic frontal QRS-T angle and survival in patients with heart failure. PLoS One. 2018;13(3):e0194520.

9. Kim BJ, Park HS, Im SI, Kim HS, Heo JH, Cha TJ et al. Changes in QRS duration are associated with a therapeutic response to sacubitril-valsartan in heart failure with reduced ejection fraction. J Cardiovasc Imaging. 2020;28(4):244-253.

10. Aly A, Shehata H, Allam L, Eldamanhoury H. Effect of sacubitril/valsartan combination on abnormal ECG findings in patients with heart failure with reduced ejection fraction, QJM. 2017;117(Suppl 1).

11. Bazett H. An analysis of the time-relations of the electrocardiograms. Heart. 1920;7:353-370.

12. Gotsman I, Keren A, Hellman Y, Banker J, Lotan C, Zwas DR. Usefulness of electrocardiographic frontal QRS-T angle to predict increased morbidity and mortality in patients with chronic heart failure. Am J Cardiol. 2013;111(10):1452-1459.

13. Chauhan VS, Downar E, Nanthakumar K, Parker JD, Ross HJ, Chan W, et al. Increased ventricular repolarization heterogeneity in patients with ventricular arrhythmia vulnerability and cardiomyopathy: a human in vivo study. Am J Physiol Heart Circ Physiol. 2006;290(1):H79-H86.

14. Callans DJ, Donahue JK. Repolarization heterogeneity in human post-infarct ventricular tachycardia. JACC Clin Electrophysiol. 2022;8(6):713-718.

15. Ilkhanoff L, Qian X, Lima JA, Tran H, Soliman EZ, Yeboah J, et al. Electrocardiographic associations of cardiac biomarkers and cardiac magnetic resonance measures of fibrosis in the multiethnic study of atherosclerosis (MESA). Am J Cardiol. 2023;204:287-294.

16. Januzzi JL Jr, Prescott MF, Butler J, Felker GM, Maisel AS, McCague K, et al. Association of change in N-terminal pro-B-type natriuretic peptide following initiation of sacubitril-valsartan treatment with cardiac structure and function in patients with heart failure with reduced ejection fraction. JAMA. 2019;322(11):1085-1095.

17. Tsai YN, Cheng WH, Chang YT, Hsiao YW, Chang TY, Hsieh YC, et al. Mechanism of angiotensin receptor-neprilysin inhibitor in suppression of ventricular arrhythmia. J Cardiol. 2021;78(4):275-284.

18. Algül E, Özbeyaz NB, Şahan HF, Aydınyılmaz F, Gezer E, Sunman H, et al. Frontal QRS - T angle is associated with severity and prognosis of acute pulmonary embolism. J Electrocardiol. 2023;79:8-12.

19. Chen S, Hoss S, Zeniou V, Shauer A, Admon D, Zwas DR, et al. Electrocardiographic predictors of morbidity and mortality in patients with acute myocarditis: the importance of QRS-T angle. J Card Fail. 2018;24(1):3-8.

20. Zadeh B, Wambach JM, Lambers M, Nassenstein K, Jensen CJ, Bruder O. QRS-T-angle in patients with ST-segment elevation myocardial infarction (STEMI) - a comparison with cardiac magnetic resonance imaging. Int J Med Sci. 2020;17(15):2264-2268.

21. Raposeiras-Roubín S, Virgós-Lamela A, Bouzas-Cruz N, López-López A, Castiñeira-Busto M, Fernández-Garda R, et al. Usefulness of the QRS-T angle to improve long-term risk stratification of patients with acute myocardial infarction and depressed left ventricular ejection fraction. Am J Cardiol. 2014;113(8):1312-1319.

22. Dhingra R, Pencina MJ, Wang TJ, Nam BH, Benjamin EJ, Levy D, et al. Electrocardiographic QRS duration and the risk of congestive heart failure: the Framingham heart study. Hypertension. 2006;47(5):861-867.

23. Kashani A, Barold SS. Significance of QRS complex duration in patients with heart failure. J Am Coll Cardiol. 2005;46:2183-2192.

24. Bode-Schnurbus L, Böcker D, Block M, Gradaus R, Heinecke A, Breithardt G, et al. QRS duration: a simple marker for predicting cardiac mortality in ICD patients with heart failure. Heart. 2003;89(10):1157-1162.

25. Shamim W, Yousufuddin M, Cicoria M, Gibson DG, Coats AJ, Henein MY. Incremental changes in QRS duration in serial ECGs over time identify high risk elderly patients with heart failure. Heart. 2002;88(1):47-51.