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RISK STRATIFICATION FOR VENTRICULAR TACHYARRHYTHMIAS AFTER CARDIOVERTER-DEFIBRILLATOR IMPLANTATION FOR PRIMARY PREVENTION OF SUDDEN CARDIAC DEATH: RESULTS OF THE IDEAL SINGLE-CENTER PROSPECTIVE STUDY

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Aim. The aim of this study was to develop additional selection criteria for implanted cardioverter-defibrillator (ICD) implantation in the primary prevention of sudden cardiac death (SCD) based on the risk stratification for the development of sustained ventricular tachycardia (VT).

Methods. The study included 451 patients with heart failure and reduced left ventricular ejection fraction (HFrEF) who were referred for ICD implantation for primary prevention of SCD. Participants underwent pre-implantation screening of clinical, instrumental, and laboratory parameters, followed by prospective observation for 24 months to record the first occurrence of sustained VT or justified ICD therapy. To achieve the study's goal, training and test samples were formed.

Results. The arrhythmic endpoint was recorded in 84 patients (26%) in the training group and in 35 patients (27%) in the test group. Univariate analysis identified 11 factors with the highest predictive potential ($p<0.1$) associated with the occurrence of the studied endpoint. These included clinical data: coronary artery disease, arterial hypertension, resting heart rate >80 bpm; electrocardiographic parameters: complete left bundle branch block according to Strauss criteria, P-wave duration (lead II) >120 ms, or the presence of atrial fibrillation (in the case of persistent form), index of cardiac electrophysiological balance (ICEB) >3.1; echocardiographic parameters: presence of eccentric left ventricular hypertrophy, global longitudinal strain ≥ minus 6%; laboratory markers: galectin-3 >12 ng/ml, sST-2 >35 ng/ml, NT-proBNP >2000 pg/ml. Based on the regression coefficients, points were assigned to each factor, and the sum of these points determined the value of a new proposed index - the arrhythmic risk index (ARI). ARI values >5 points predicted the two-year likelihood of VT in HFrEF patients with a sensitivity of 78.6% and specificity of 64.3% (AUC=0.788±0.028 with 95% confidence interval (CI): 0.732-0.843; p=0.0001). The application of ARI in the test group demonstrated good model performance in predicting two-year VT risk (AUC=0.652±0.053 with 95% CI: 0.547-0.757; p=0.008).

Conclusion. Based on the obtained results, a predictive index was developed, allowing for personalized and timely risk assessment of VT in patients with HFrEF.

Key words: chronic heart failure; prediction; ventricular tachyarrhythmias; sudden cardiac death; implantable cardioverter-defibrillators

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Sudden cardiac death (SCD), alongside critical cardiac decompensation, is a leading cause of cardiovascular mortality in patients with heart failure with reduced ejection fraction (HFrEF) of the left ventricle (LV). SCD is defined as natural death due to cardiac pathology, preceded by sudden loss of consciousness within one hour of the onset of acute symptoms, where prior heart disease may be known but the occurrence of death is unexpected

[1]. The term “sudden cardiac death” is based on a specific mechanism of death rather than a specific cause. In the vast majority of cases, the mechanism of circulatory arrest is ventricular tachyarrhythmias (VT) [2].

The predominantly arrhythmogenic nature of SCD forms the basis for its prevention using implantable cardioverter-defibrillators (ICDs). Today, ICDs should be regarded as the primary tool for both primary and secondary prevention of SCD, with a strong evidence base and high-level indications [3, 4]. Randomized controlled trials have demonstrated the effectiveness of ICDs in the primary prevention of SCD in patients with chronic heart failure (CHF) and an LV ejection fraction (LVEF) ≤35% [5, 6].

However, many experts believe that determining indications for interventional primary prevention of SCD solely based on LVEF requires reconsideration. Consequently, the search for new predictors to identify very high-risk groups for SCD among HFrEF patients is considered a pressing and necessary task. Currently, diagnostic tools aimed at identifying potential morphological and electrophysiological substrates required for the realization of the arrhythmogenic SCD scenario are seen as the most promising [7]. The presence of such arrhythmogenic potential can be inferred from prolonged or shortened corrected QT interval (QTcor) on electrocardiograms, changes in the interval from the peak to the end of the T wave (TpTe) [8, 9], and voltage criteria for LV hypertrophy (LVH) [10]. A simple, non-invasive method for diagnosing and monitoring myocardial fibrosis is the measurement of circulating profibrogenic biological agents in the blood, which may serve as indicators of risk for adverse clinical events, including SCD [11].

Risk stratification for fatal ventricular arrhythmias can also be aided by transthoracic echocardiographic (EchoCG) parameters [12], two-dimensional myocardial strain imaging [13], and myocardial contrast imaging with gadolinium chelates during cardiac magnetic resonance imaging (MRI) [14]

A multifactorial approach to VT risk assessment has been advocated. H.T. Reeder et al., based on secondary analysis of data from the SCD HEFT (Sudden Cardiac Death in Heart Failure Trial), proposed a regression model for predicting ICD-delivered electrical therapy, which included atrial fibrillation (AF), diabetes mellitus, coronary artery disease (CAD), blood creatinine and sodium levels, age, CHF functional class, and LVEF [15]. J. Lupon et al. included age, gender, LVEF, CHF duration, and biochemical markers (eGFR and ST2) in their predictive model for estimating the five-year risk of SCD [16]. The intensity of gadolinium uptake on cardiac MRI, age, history of syncope, AF/flutter, nonsustained VT, and AV block formed the basis of the ESTIMATED index developed by Chinese researchers for VT risk stratification in patients with non-ischemic CHF [17]. However, even such a comprehensive approach has not led to a significant improvement in VT risk stratification in HFrEF patients, highlighting the need for continued research in this area.

Aim of the study: to develop additional selection criteria for ICD implantation for the primary prevention of SCD based on risk stratification for sustained VT.

METHODS

The data presented in this article were obtained from the completed single-center prospective IDEAL study. The detailed study design is available in the public registry at clinicaltrials.gov (NCT05539898). Inclusion criteria were the current indications for ICD implantation for primary prevention of SCD [2]: CHF of NYHA functional class II-III with an LVEF ≤35% on optimal medical therapy for at least six months. Mandatory inclusion criteria included the completion of maximal myocardial revascularization (if indicated).

Exclusion criteria: Hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia, confirmed hereditary channelopathies, indications for cardiac surgery (revascularization, valve insufficiency correction), documented sustained VT episodes, family history of SCD, history of syncope, or previous SCD episodes [18].

The study design is shown in Figure 1. Patient selection was conducted between 2012 and 2021. After evaluating inclusion and exclusion criteria, a standard clinical examination was performed according to the CHF diagnostic algorithm. Additional assessments included speckle-tracking EchoCG and blood biomarker measurements (electrolytes, C-reactive protein, creatinine, soluble suppressor of tumorigenesis-2 [sST-2], NT-proBNP, galectin-3). Glomerular filtration rate (GFR) was calculated using the CKD-EPI formula (Chronic Kidney Disease Epidemiology Collaboration) based on serum creatinine levels.

All included patients received dual-chamber ICDs or ICDs with cardiac resynchronization therapy (CRT-D) as a means of primary SCD prevention. Participants were prospectively observed for 24 months post-ICD implantation

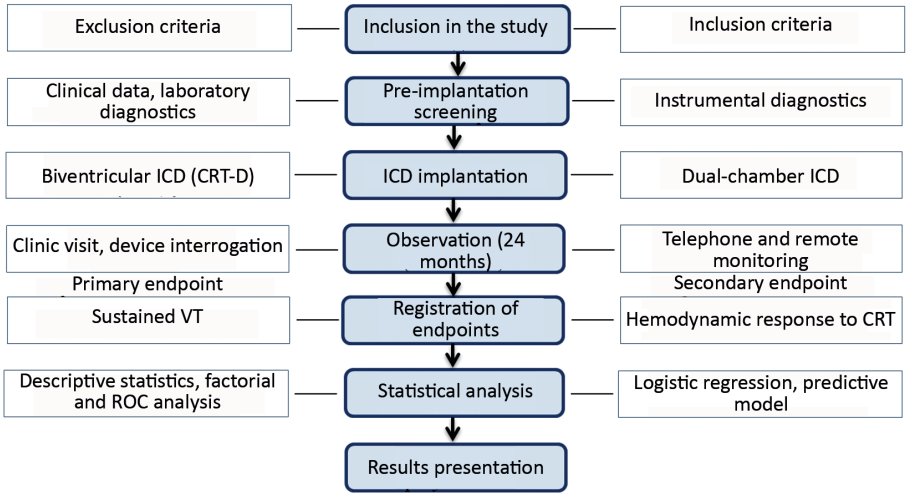

Figure 1. Flow chart illustrating the study design. Abbreviations: VT - ventricular tachyarrhythmia; ICD - implantable cardioverter-defibrillator; CRT-D - implantable cardioverter-defibrillator with cardiac resynchronisation therapy function.

by cardiologists at their local facilities and at the implanting center. This follow-up ensured proper monitoring of medical therapy and the registration of study endpoints.

The primary endpoint was the first occurrence of a sustained VT episode (≥30 seconds), detected in the VT "monitor" zone or requiring electrical therapy (antitachycardia pacing or shock therapy) during the two-year observation period. Hemodynamic response to CRT was also evaluated. According to previous findings, an LVEF improvement of ≥5% is sensitive to arrhythmic risk modification [8]. The same approach was applied to assess CRT response concerning the study endpoint.

Statistical Analysis

Subsequent statistical analysis was performed using methods aligned with the study's objectives. The research methods, including statistical techniques, have been described in earlier publications [19-21]. IBM SPSS Statistics 26 and Jamovi 2.3.28 software were used for generat-

Table 1.

Comparative characteristics of patients in the training and test cohorts

Clinical indicator	Training cohort (n=319)	Test cohort (n=132)	p
Age, years	57 (51-63)	57 (52-61)	0.557
Male sex, n (%)	265 (83)	106 (80)	0.484
Body mass index, kg/m^2	28.7 (25.4-32.5)	29.3 (25.7-32.7)	0.646
Coronary artery disease, n (%)	160 (50)	59 (45)	0.291
Post-infarction cardiosclerosis*, n (%)	118 (37)	44 (34)	0.480
Non-ischaemic cardiomyopathy, n (%)	159 (50)	73 (55)	0.291
Coronary artery lesions#, n (%)	132 (41)	65 (49)	0.126
Chronic heart failure II FC, n (%)	22 (7)	5 (4)	0.201
Chronic heart failure III FC, n (%)	233 (74)	95 (72)	0.739
History of arterial hypertension, n (%)	180 (56)	69 (52)	0.420
Diabetes mellitus, n (%)	61 (19)	26 (20)	0.888
History of obesity	119 (37)	46 (35)	0.622
Stroke, n (%)	20 (6)	11 (8)	0.431
Chronic kidney disease, n (%)	139 (46)	50 (41)	0.379
AF (paroxysmal/persistent), n (%)	90 (28)	41 (31)	0.544
AF (permanent), n (%)	26 (8)	9 (7)	0.618
History of non-sustained ventricular tachycardia, n (%)	43 (13)	10 (8)	0.076
Systolic blood pressure, mmHg	120 (110-130)	120 (110-130)	0.294
Diastolic blood pressure, mmHg	80 (70-80)	80 (70-80)	0.289
Heart rate, bpm	78 (68-90)	78 (68-88)	0.976
NT-proBNP, pg/ml	2446 (1350-5049)	2683 (1409-4958)	0.782
Glomerular filtration rate (CKD EPI), ml/min/1.73 m^2	67 (58-77)	67 (63-76)	0.092
Cardiac surgeries			
Revascularisation&, n (%)	134 (42)	50 (38)	0.361
Valve insufficiency correction, n (%)	62 (20)	25 (19)	0.856
Left ventricular repair, n (%)	29 (9)	8 (6)	0.271
Echocardiographic indicators			
Left ventricular end-diastolic volume, ml	230 (198-288)	223 (182-280)	0.339
Left ventricular end-systolic volume, ml	162 (135-204)	158 (131-198)	0.431
Left ventricular end-diastolic dimension, cm	6.7 (6.3-7.4)	6.6 (6.1-7.2)	0.250
Left ventricular end-systolic dimension, mm	5.8 (5.2-6.5)	5.6 (5.1-6.3)	0.481
Left ventricular ejection fraction (Simpson), %	29 (24-33)	29 (25-34)	0.355
Implanted cardioverter-defibrillator			
Cardioverter-defibrillator with CRT function, n (%)	190 (60)	78 (59)	0.926
Dual-chamber cardioverter-defibrillator, n (%)	129 (40)	54 (41)	0.926

Note: hereinafter, * - among patients with coronary artery disease; # in patients with non-ischaemic cardiomyopathy; FC - functional class; AF - atrial fibrillation; & - coronary artery bypass grafting or percutaneous coronary intervention; CRT - cardiac resynchronisation therapy.

ing graphs and charts to illustrate results. Data in tables are presented as absolute patient counts (%) or as Me (Q1-Q3), unless otherwise stated.

Sample size calculations for statistically significant results in logistic regression were performed using GPower 3.1.9.4 software with a priori power calculation for z-tests. Input parameters included two-sided asymptotic significance, $\alpha = 0.05$, $\beta = 20\%$, yielding a study power of 80%, binomial distribution, balanced model ($\pi = 0.5$), and a correction for interaction among independent factors of 0.1 (for R^2). Sample size calculations assessed the impact of each predictor on outcomes. The odds of the outcome occurring in the study group were 2.5 times higher than in the control group for the predictor "Presence of coronary artery disease" (odds ratio [OR] 2.2; 95% confidence interval [CI]: 1.2-5.1) [22]. With these parameters, the sample size required was 214 participants. To achieve the study's objectives, a total of at least 450 patients were planned to be included, divided into two groups: training and testing cohorts.

RESULTS

Clinical and demographic characteristics of patients undergoing prospective observation

After screening for inclusion and exclusion criteria, 539 patients were enrolled in the study. During the two-year follow-up, 88 patients were excluded for various reasons (loss of contact - 71 patients, non-cardiac deaths - 12 patients, and heart transplantation - 5 patients). The final cohort included 451 CHF patients with NYHA class II-III and an LVEF of 29 (25-33)%. The majority of patients were male (371 patients, 82%) of working age - 57 (51-62) years.

Before study enrollment, patients underwent maximal possible myocardial revascularization (184 patients, 41%), and valve pathology correction was performed if indicated (87 patients, 19%). All patients received optimal medical therapy for CHF in accordance with current clinical guidelines at the time of inclusion. During prospective follow-up, medical therapy was adjusted based on clinical status and opportunities to introduce new CHF medications. Quadritherapy, as per the 2020 CHF treatment recommendations, was prioritised [23].

At the end of the follow-up period, patients were divided into two groups: a training sample, used to identify prognostic factors and develop multifactorial prognostic models, and a test sample, used to validate the accuracy of predictions for the studied endpoints. Groups were formed through random selection in a 70:30 ratio. These groups did not differ significantly in key clinical-demographic parameters or known risk factors for the studied endpoints (Tables 1 and 2).

Incidence of the primary endpoint and clinical predictors of VT

During the two-year follow-up, the arrhythmic endpoint was observed in 84 patients (26%). Groups were comparable in most clinical-demographic characteristics based on endpoint achievement.

Coronary artery disease (CAD) with stenosis >30% was an important prognostic factor for VT in both non-ischemic cardiomyopathy (NICM) (OR 3.23; 95% CI: 0.99-10.54; p=0.052) and ischemic cardiomyopathy (ICM) (OR 4.61; 95% CI: 1.44-14.79; p=0.010). Kaplan-Meier survival analysis showed earlier clinically significant first VT episodes in CAD patients. Median freedom from VT was 19.7 (95% CI: 18.6-20.9) months in CAD patients and 21.6 (95% CI: 20.8-22.5) months in NICM patients (p=0.036).

Electrocardiographic Predictors of VT

Before ICD implantation, most patients had sinus rhythm (81%). The cohort was characterised by leftward electrical axis deviation (71%), voltage signs of LVH (62%), interatrial conduction disturbances (P-wave duration - 120 [101-120] ms), and prolonged ventricular electrical systole (QTcor - 465 [438-498] ms).

Patients without VT had longer QRS durations (p=0.01) and more frequent complete left bundle branch block (LBBB) (p=0.004). VT patients showed a higher index of cardiac electrophysiological balance (ICEB) (p=0.033). An ICEB cutoff >3.1 correlated with increased VT risk (OR 1.67; 95% CI: 1.01-2.76; p=0.044). P-wave durations >120 ms doubled VT risk (OR 2.10; 95% CI: 1.09-4.07; p=0.026).

Echocardiographic Predictors of VT

Both groups exhibited significant increases in the linear and volumetric dimensions of the LV and reductions in LVEF. The echocardiographic parameters indicated pathological LV remodeling, predominantly of the eccentric hypertrophy type (78%). Patients free of VT were more likely to have LV remodeling consistent with eccentric hypertrophy (83% vs. 66%; p=0.002), whereas patients with VT more frequently exhibited concentric LV hypertrophy (13% vs. 6%; p=0.053) with increased posterior wall thickness (p=0.016).

In all patients who underwent speckle-tracking echocardiography (n=133), significant shifts in longitudinal strain parameters were detected across most LV myocardial segments. Comparative analysis of peak systolic longitudinal strain values revealed worse deformation characteristics in the LV segments corresponding to the inferior and anterior walls in VT patients (p=0.001) (Figure 2).

Table 2.

Medication therapy in patients from the training and test cohort

	Training cohort (n=319)	Test cohort (n=132)	p
β-blockers, n (%)	451 (100)	451 (100)	-
ACEI/ ARB, n (%)	218 (68)	87 (66)	0.616
ARNI, n (%)	111 (35)	43 (33)	0.651
MRA, n (%)	283 (89)	114 (86)	0.484
Loop diuretics, n (%)	311 (98)	125 (95)	0.132
SGLT2 inhibitors, n (%)	52 (16)	21 (16)	0.918
Amiodarone, n (%)	123 (39)	51 (39)	0.717

Note: hereinafter, ACEI - angiotensin-converting enzyme inhibitors; ARNI - angiotensin receptor-neprilysin inhibitors; MRA - mineralocorticoid receptor antagonists; ARB - angiotensin receptor blockers; SGLT2 - sodium-glucose cotransporter 2.

The arrhythmic endpoint was directly associated with global longitudinal strain (GLS): VT patients demonstrated lower absolute GLS values, indicative of worse longitudinal LV deformation. ROC analysis was performed to determine the critical GLS cutoff value. The area under the ROC curve (AUC) was 0.664 ± 0.061 (95% CI: 0.544-0.783). A GLS cutoff of -6% predicted the first VT manifestation with 44% sensitivity and 76% specificity. It was found that GLS values <-6% increased the risk of the first VT manifestation during the observation period by almost threefold (OR 2.59; 95% CI: 1.07-6.26; p=0.031). Differences in global circumferential strain values were close to significance (p=0.055).

Using the same cutoff value (<-6%) for regional strains, it was observed that impaired longitudinal deformation in the anterior segments increased VT risk by 3.5 times (OR 3.57; 95% CI: 1.40-9.09; p=0.006), while impairment in the inferior segments increased the risk nearly eightfold (OR 7.67; 95% CI: 2.75-21.38; p=0.0001).

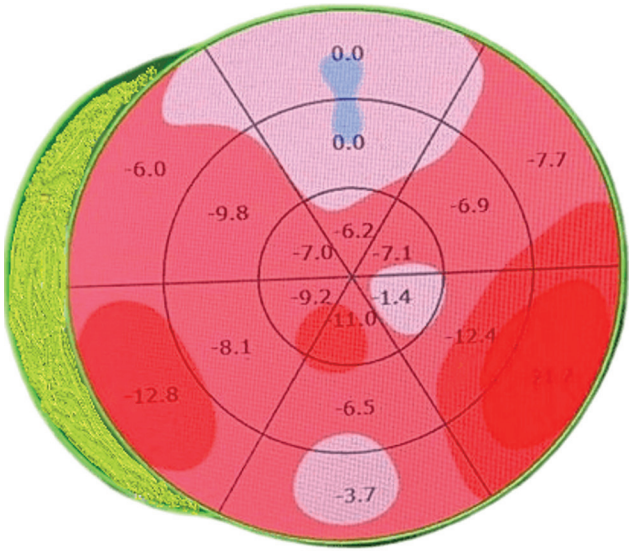

Figure 2. Distribution pattern of regional longitudinal strain on the 18-segment left ventricular model («bull's eye») before ICD implantation in a patient with ventricular tachycardia registered during follow-up. Amidst diffuse longitudinal strain reduction, the poorest myocardial longitudinal strain parameters of the left ventricle were observed in the anterior and inferior segments.

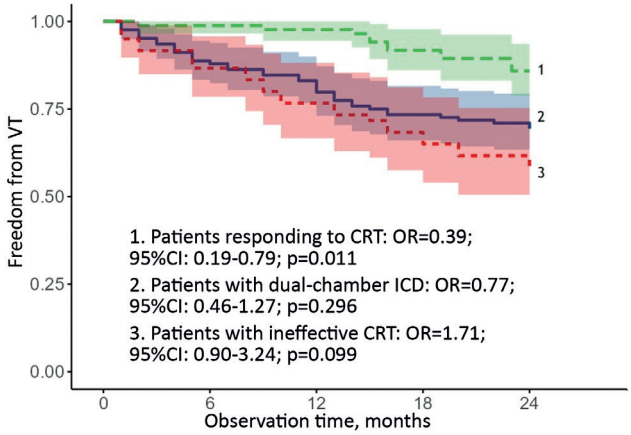

Figure 3. Kaplan-Meier curve illustrating the incidence of the arrhythmic endpoint depending on the application and effectiveness of cardiac resynchronisation therapy (CRT). Abbreviations: VT - ventricular tachyarrhythmia; ICD - implantable cardioverter-defibrillator; CRT - cardiac resynchronisation therapy.

Biomarkers Indicating VT Risk

Analysis of blood biomarkers revealed significant differences in NT-proBNP and sST-2 concentrations (p=0.001 and p=0.021, respectively). The difference in galectin-3 levels was close to statistical significance (p=0.066). ROC analysis was performed to determine critical thresholds for these quantitative predictors (p<0.05). It was found that sST-2 >35 ng/mL increased the risk of the first VT manifestation during the observation period nearly threefold (OR 2.86; 95% CI: 1.23-6.64; p=0.013). Similarly, galectin-3 >12 ng/mL had comparable prognostic significance (OR 2.64; 95% CI: 1.06-6.53; p=0.032). Conversely, NT-proBNP >2000 pg/mL was associated with a 2.2-fold lower risk for the same outcome (OR 0.46; 95% CI: 0.22-0.95; p=0.034). In groups with elevated levels of these biomarkers, the median time to VT was earlier: 18.7 (0.8) months (95% CI: 19.8-22.8 months) for sST-2 >35 ng/mL and 19.1 (0.9) months (95% CI: 17.4-20.8 months) for galectin-3 >12 ng/mL.

Effect of CRT on VT Risk

In the CRT-D group, CRT was effective in 112 patients (59%), with LVEF improving from 27 (22-32)% to 39 (34-45)% (p=0.0001). Absolute LVEF improvement was as follows: ≤35% in 45 patients (40%), 36-40% in 21 patients (19%), and >40% in 46 patients (41%). VT incidence was significantly lower in patients who responded to CRT (14% vs. 42% in the non-responders). The impact of effective CRT on arrhythmic risk was further supported by survival analysis (Figure 3).

The data demonstrated that an LVEF increase of ≥5% reduced VT risk fourfold (OR 0.23; 95% CI: 0.10-0.51; p=0.0001). A more pronounced hemodynamic response to CRT was observed in patients without VT. However, CRT alone, without consideration of its effectiveness, did not show a significant impact on arrhythmic endpoints (OR 0.77; 95% CI: 0.46-1.27; p=0.296).

Multivariate Analysis of VT Predictors and Prognostic Models

Univariate analysis identified 11 factors with high predictive potential (p<0.1) related to the primary endpoint. Based on these factors, binary logistic regression was used to develop prognostic models for predicting the two-year likelihood of VT in HFrEF patients. The best regression model (Table 3), with optimal sensitivity and specificity, was statistically significant (p=0.001). The Nagelkerke coefficient of determination indicated that 32.1% of the variance in VT probability was explained by the studied factors.

Diagnostic performance, at a regression function cutoff of 0.257, was 74.6% (sensitivity - 74.7%; specificity - 74.5%). The area under the ROC curve (AUC) for the two-year VT prediction was 0.802, indicating excellent model quality.

Most parameters showed a direct relationship with VT probability, except "presence of LBBB per Strauss criteria," "eccentric LV hypertrophy," and "NT-proBNP >2000 pg/mL," which had an inverse relationship. Based

on calculated β-coefficients, scores were assigned to each factor, and their sum determined a new proposed index-the Arrhythmic Risk Index (ARI) (Table 4). ROC analysis established a threshold value of 5 points for ARI. ARI >5 points predicted the two-year VT probability in HFrEF patients with a sensitivity of 78.6% and specificity of 64.3% (AUC=0.788 ± 0.028; 95% CI: 0.732-0.843; p=0.0001).

Validation in Test Cohort

Applying ARI in the test cohort demonstrated good model performance for predicting two-year VT risk (AUC=0.652 ± 0.053; 95% CI: 0.547-0.757; p=0.008). Each 1-point increase in ARI raised VT risk by 1.08 times (95% CI: 1.02-1.15; p=0.015). ARI >5 points increased the two-year VT risk fourfold (OR 4.04; 95% CI: 1.77-9.24; p=0.001) with 68.6% sensitivity and 64.9% specificity. Among high-risk VT patients (ARI >5 points, n=58), the arrhythmic endpoint was observed in 41% (24 patients) during the two-year follow-up, compared to 15% (11 patients) in the low-risk group (ARI ≤5 points, n=74) (Figure 4).

DISCUSSION

During the two-year observation period, the arrhythmic endpoint was registered in 84 patients (26%). Overall, many experts have noted a global trend of decreasing ICD electrical therapy activation rates [24]. This trend can be attributed to two main factors. First, the evolution of device programming strategies, including prolonged episode detection durations and higher detection thresholds for VT zones requiring active electrical therapy. Second, changes in the clinical profiles of HFrEF patients due to advancements in pharmacological and interventional cardiovascular therapies, as well as improved preventive measures. Consequently, the applicability of findings from earlier studies may need reevaluation, and the prediction of adverse outcomes, including VT risk, should rely on data derived from contemporary HFrEF cohorts.

The limitations of the current SCD risk stratification system, which is based solely on LVEF, are highlighted by several studies. For example, the DANISH trial demonstrated that ICD implantation for primary prevention of SCD in patients with symptomatic CHF of non-ischemic origin did not reduce mortality in those receiving modern CHF therapy [25]. As a result, ICDs are not always implanted in patients with the most urgent need. Additionally, the high cost of this procedure and the necessity for device replacement (reimplantation) every 4-5 years, accompanied by risks such as system infections and infective endocarditis, underscore the need for improved selection criteria for ICD implantation. The most likely solution to this problem is supplementing the current single-factor SCD risk stratification system with new VT predictors [26] and developing effective multifactorial prognostic systems to predict the risk of the first VT episode in HFrEF patients.

Together with this, it would be incorrect to claim that efforts to develop such systems have not been made earlier. For instance, X. Li et al. proposed assessing ICD utility based on VT risk stratification in NICM patients using the ESTIMATED scale (LGE-Based Prediction of SCD Risk in Nonischemic Dilated Cardiomyopathy), which involves quantifying gadolinium accumulation in the myocardium during cardiac MRI [17].

The Seattle Heart Failure Model (SHFM), a prognostic calculator for predicting CHF survival, also deserves mention [27]. The SHFM-D modification (D - Differentiated ICD Benefit), supplemented with data on digoxin and carvedilol use and serum creatinine levels, was designed to stratify patients by the anticipated benefit from ICD implantation [28]. However, it is important to note that SHFM was developed and validated using data from ambulatory patients. Its applicability to hospitalized patients with severe comorbidities (e.g., liver cirrhosis, renal failure, dementia, or cancer) remains questionable.

The MUSIC scale (MUerte Subita en Insuficiencia Cardiaca) allows risk estimation for all-cause mortality, cardiovascular mortality, and SCD based on individual predictors [29]. Notably, some predictors proposed by R. Vazquez et al.-such as AF, CLBBB, and NT-proBNP

Table 3.

Proposed predictors of ventricular tachyarrhythmias

	Univariate analysis			Multivariate analysis		
	OR	95% CI	P	OR	95% CI	P
Clinical predictors						
Presence of CA lesions	3.50	1.20-14.96	0.044	4.59	1.04-34.71	0.078
History of AH	1.56	0.94-2.63	0.092	1.61	0.84-3.13	0.155
HR >80 bpm	1.75	1.05-2.90	0.030	1.65	0.88-3.09	0.117
Electrocardiographic predictors						
P-wave duration >120 ms*	2.96	1.59-5.48	0.001	3.15	1.43-7.06	0.005
CLBBB by Strauss	0.43	0.24-0.76	0.004	0.57	0.23-1.37	0.208
ICEB >3.1	2.01	1.22-3.34	0.007	1.31	0.59-3.00	0.512
Echocardiographic predictors						
Eccentric LVH	0.42	0.23-0.77	0.005	0.26	0.13-0.53	0.001
GLS value <6%	3.06	1.48-6.29	0.002	2.03	0.78-5.20	0.141
Laboratory Ppedictors						
Galectin-3 >12 ng/mL	2.70	1.29-6.39	0.014	3.06	1.20-9.15	0.029
sST-2 >35 ng/mL	3.24	1.78-5.89	0.001	2.44	1.16-5.13	0.018
NT-proBNP >2000 pg/mL	0.28	0.15-0.54	0.001	0.27	0.12-0.58	0.001

Note: hereinafter, OR - odds ratio; CI - confidence interval; CA - coronary arteries; AH - arterial hypertension; HR - heart rate; * - in lead II or permanent atrial fibrillation; CLBBB - complete left bundle branch block; ICEB - index of cardiac electrophysiological balance; LVH - left ventricular hypertrophy; GLS - global longitudinal strain; sST-2 - soluble isoform of tumour suppressor-2; NT-proBNP - N-terminal pro-brain natriuretic peptide.

>1000 pg/mL-are also included in the prognostic scales developed in this study.

Findings from external validation of the MAGGIC scale (The Meta-Analysis Global Group in Chronic Heart Failure) in a retrospective study by M. Canera et al. (1,089 HFrEF patients with ICDs) showed low prognostic accuracy for SCD risk, defined either as any ICD therapy (AUC=0.53; 95% CI: 0.49-0.57) or as a VT episode requiring appropriate shock therapy (AUC=0.52; 95% CI: 0.45-0.59).

L. Shen et al., based on large trials such as PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) and ATMOSPHERE (The Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure), developed predictive models that showed good potential for SCD risk assessment (AUC=0.68) [30]. The authors highlighted two key predictors: NT-proBNP concentration and CHF functional class, both significantly influencing adverse outcome probability. Interestingly, prolonged QRS duration was an SCD marker (OR=1.07; 95% CI: 1.03-1.11 per 5 ms above 120 ms). This finding, however, contrasts with results from this study, likely due to low CRT use among the studied patients (CLBBB prevalence in PARADIGM-HF: 20.1%; in ATMOSPHERE: 21.1%; CRT devices implanted in PARADIGM-HF: 1.9%; in ATMOSPHERE: 1.8%).

In 2020, U.S. researchers developed the MADIT-ICD Benefit Score calculator using clinical data and endpoint information from four MADIT studies-MADIT-2 [5], MADIT-CRT [31], MADIT-RIT [32], and MADIT-RISK-with over 4,500 CHF patients [33]. Accounting for VT or nonarrhythmic death probability, the calculator provides information on ICD benefit levels. Results from ROC analysis after external validation indicated additional prognostic value (C-statistic for VT prediction: 0.75; for nonarrhythmic death prediction: 0.67). However, the calculator was developed using MADIT data collected between 2002 and 2012, and external validation was based on the RAID study, completed in 2017 [34]. Advances in optimal medical therapy since then may limit the MADIT-ICD Benefit Score's effectiveness for CHF outcome prediction [35].

Table 4.

Results of binary logistic regression for predicting the occurrence of VT with conversion of the obtained β-coefficients into scores

Predictor	β-coefficient	Points
Presence of CA lesions	1.523	6
History of AH	0.473	2
HR >80 bpm	0.499	2
P-wave duration >120 ms*	1.147	4
CLBBB by Strauss	-0.566	-2
ICEB >3.1	0.271	1
Presence of ecentric LVH	-1.338	-5
Absolute GLS value <6%	0.707	3
Galectin-3 >12 ng/mL	1.118	4
sST-2 >35 ng/mL	0.890	3
NT-proBNP >2000 pg/mL	-1.319	-5

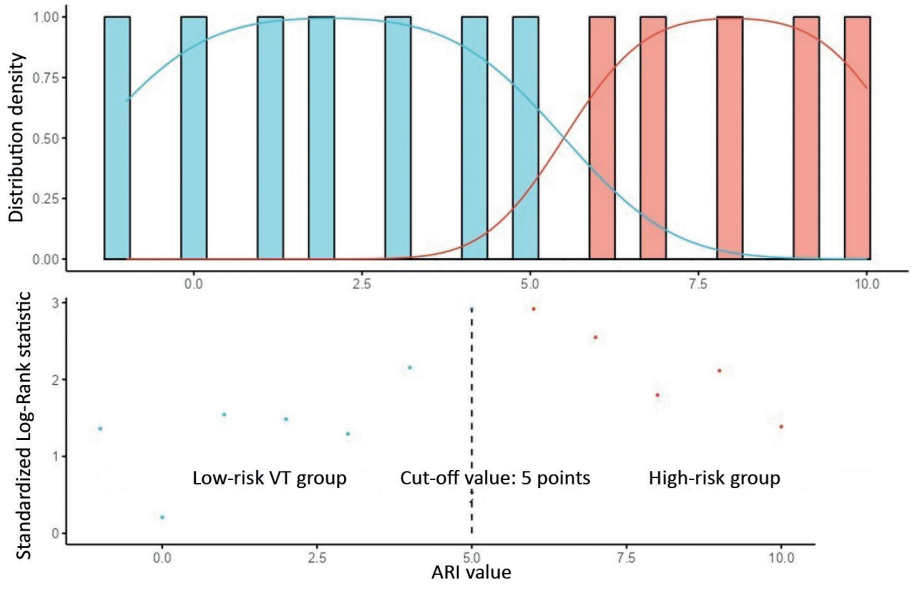

Figure 4. Risk stratification for ventricular tachyarrhythmias (VT) in the test cohort based on the arrhythmic risk index (ARI) values.

The need for external validation of proposed multifactorial prognostic systems across diverse cohorts and ethnic groups cannot be overstated. Despite high diagnostic potential described in original studies, no known prognostic algorithm has yet been incorporated into CHF care standards [23]. This highlights the clinical and economic relevance of improving patient selection criteria for ICD implantation.

Thus, despite substantial clinical material underpinning these conclusions, practical applicability remains uncertain. A key advantage of the prognostic index proposed in this study is its use of well-established clinical factors (e.g., a history of hypertension, coronary artery disease, resting heart rate values) and advanced diagnostics. These include assessments of contemporary blood biomarkers (sST-2, galectin-3), individual electrophysiological status (e.g., intraventricular and atrial conduction disturbances, ICEB), and myocardial deformation properties at both regional and global levels.

Study limitations

A limitation of this study is its single-centre design. The results indicate a lower rate of CRT responders compared to other researchers' findings. It should be emphasised that patient recruitment began in 2012, meaning CRT response may not have been achieved in some cases due to various objective factors, including suboptimal delivery systems, the absence of quadripolar electrodes for

LV pacing, and programming limitations of the implanted devices. The registration frequency of the endpoints might also have been influenced by the introduction of new CHF therapies with antiarrhythmic effects.

Considering the extended follow-up period and the absence of strict monitoring tasks for the prescribed therapies or their impact on endpoints, it is impossible to determine how many patients received CHF quadruple therapy and at what stage of prospective observation. While the lack of quadruple therapy in all patients represents a limitation of the study, it also reflects real-world clinical practice, where the full implementation of CHF quadruple therapy is often unattainable, particularly due to severe arterial hypotension.

CONCLUSION

The study demonstrated the potential for personalised risk assessment of VT. The strategic significance of the proposed multi-marker index lies in its applicability both under comprehensive evaluation of all specified predictors and in settings with limited diagnostic resources, which is particularly relevant for regional healthcare systems.

An important conclusion of the study is the evidence that patients with HFrEF, who have the same class of indication for ICD implantation for primary prevention of SCD according to current clinical guidelines, differ in their arrhythmic risk. This distinction must be considered when developing personalised management strategies for patients with HFrEF.

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