PREDICTORS OF RECURRENCE OF SUDDEN CARDIAC ARREST IN PATIENTS TREATED WITH AN IMPLANTABLE CARDIOVERTER DEFIBRILLATOR

PREDIKTORI RECIDIVA SRČANOG ZASTOJA KOD PACIJENATA LEČENIH IMPLANTABILNIM KARDIOVERTER DEFIBRILATOROM

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Abstract

Introduction. Randomised clinical trials have demonstrated the indispensable role of implantable cardioverter defibrillators in reducing mortality among patients at high risk of sudden cardiac death. This study aimed to assess the incidence and predictors of cardiac arrest recurrence in such patients. **Material and Methods.** This retrospective study included 240 patients who underwent defibrillator implantation for secondary prevention at the Institute for Cardiovascular Diseases of Vojvodina between 2008 and 2020. The cumulative incidence of recurrence was determined using Kaplan–Meier curves, while Cox regression was used to identify predictors of sudden cardiac arrest recurrence. **Results.** The median follow-up was 4.46 years, and recurrence of sudden cardiac arrest occurred in 60% (n=144) of patients. Sustained ventricular tachycardia as the indication for implantation was shown to be an independent predictor of recurrence. These patients also had a significantly higher number of hospitalisations during follow-up. Patients diagnosed with channelopathy or arrhythmogenic right ventricular dysplasia had a significantly higher number of hospitalisations than those diagnosed with ischaemic or non-ischaemic cardiomyopathy. **Conclusion.** The incidence of sudden cardiac arrest recurrence following defibrillator implantation is high across all patient groups, regardless of aetiology. Sustained ventricular tachycardia as the indication for device implantation predicts a higher incidence of cardiac arrest recurrence.

Key words: Death, Sudden, Cardiac; Defibrillators, Implantable; Risk Factors; Treatment Outcome; Recurrence; Arrhythmias, Cardiac

Sažetak

Uvod. Randomizovane kliničke studije su pokazale nezamenljivu ulogu implantabilnih kardioverter defibrilatora u redukciji mortaliteta pacijenata sa visokim rizikom za iznenadnu srčanu smrt. Cilj istraživanja bio je određivanje incidencije i prediktivnih faktora recidiva iznenadnog srčanog zastoja kod ovih pacijenata. **Materijal i metode.** Sprovedena retrospektivna studija uključila je 240 pacijenata kojima je defibrilator ugrađen u Institutu za kardiovaskularne bolesti Vojvodine u periodu od 2008. do 2020. godine u cilju sekundarne prevencije. Kumulativna incidencija recidiva srčanog zastoja je procenjena korišćenjem Kaplan-Majerovih krivih, dok je Koksova regresija upotrebljena radi procene prediktivnih faktora recidiva iznenadnog srčanog zastoja. **Rezultati.** Medijana perioda praćenja bila je 4,46 godina, dok je 60% pacijenata (n = 144) imalo recidiv iznenadnog srčanog zastoja. Pokazalo se da je postojana ventrikularna tahikardija kao indikacija za ugradnju uređaja bila jedini nezavisan prediktor ponovnog srčanog zastoja. Ovi pacijenti su takođe imali značajno veći broj hospitalizacija tokom perioda praćenja. Pacijenti sa dijagnozom kanalopatije ili aritmogene displazije desne komore su imali značajno češći broj hospitalizacija u poređenju sa pacijentima sa ishemijskom ili neishemijskim kardiomiopatijama. **Zaključak.** Incidencija ponovnog srčanog zastoja nakon ugradnje implantabilnog kardioverter defibrilatora je visoka bez obzira na etiologiju. Postojana ventrikularna tahikardija kao indikacija za implantaciju uređaja predviđa veću incidenciju recidiva srčanog zastoja.

Ključne reči: srčani zastoj; implantabilni kardioverter; faktori rizika; ishod lečenja; recidivi; aritmije

Introduction

Secondary prevention of sudden cardiac death (SCD) aims to reduce the risk of SCD in patients who have survived an episode of sudden cardiac arrest (SCA) or a life-threatening arrhythmia [1]. Most cases of SCA occur in outpatient settings, with over 300,000 out-of-hospital cardiac arrests (OHCA) recorded annually in the United States, where estimated survival is 10%, falling to 6% for OHCA occurring at home [2]. Survival rates vary across European regions [3]. The aetiology of SCA and SCD differs markedly with age. In populations older than 35 years, the most common underlying pathology is coronary artery disease, accounting for approximately 65–80% of SCD cases [1,2,4,5], often as its first and only manifestation [1,2,6]. In those under 35 years, the most common pathologies are genetic structural disorders and cardiomyopathies (e.g. hereditary idiopathic dilated cardiomyopathy [IDC], hypertrophic cardiomyopathy [HCM], or arrhythmogenic right ventricular dysplasia [ARVD]), primary electrical

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Abbreviations

SCD – sudden cardiac death
SCA – sudden cardiac arrest
OHCA – out-of-hospital cardiac arrest
IDC – idiopathic dilated cardiomyopathy
HCM – hypertrophic cardiomyopathy
ARVD – arrhythmogenic right ventricular dysplasia
ICD – implantable cardioverter defibrillator
VF – ventricular fibrillation
VT – ventricular tachycardia
ICD-Tx – implantable cardioverter defibrillator therapy
ATP – anti-tachycardia pacing
LVEF – left ventricular ejection fraction
ICM – ischaemic cardiomyopathy
NICM – non-ischaemic cardiomyopathy
HFrEF – heart failure with reduced left ventricular ejection fraction
HFpEF – heart failure with preserved left ventricular ejection fraction
NIDCM – non-ischaemic dilated cardiomyopathy

disorders (e.g. long QT syndrome or Brugada syndrome), congenital heart disease, myocarditis, and other causes [1,2,5–8].

Implantable cardioverter defibrillators (ICDs) are recommended for secondary prevention of SCD in patients with documented ventricular fibrillation (VF) or haemodynamically unstable ventricular tachycardia (VT) in the absence of reversible causes, provided these arrhythmias did not occur within the first 48 hours of acute myocardial infarction [1]. ICDs continuously monitor the heart's electrical activity and deliver therapies (ICD-Tx), such as anti-tachycardia pacing (ATP) or electrical shock to terminate arrhythmia episodes meeting their pre-programmed parameters [2,9]. Randomised clinical trials have demonstrated the indispensable role of ICDs in reducing mortality among patients at high risk of SCD, regardless of the level of prevention or the underlying heart disease [10–14]. This study aimed to assess the cumulative incidence and predictors of SCA recurrence in patients with an ICD implanted for secondary prevention.

Material and Methods

This retrospective observational study included 240 patients who underwent ICD implantation at the Institute for Cardiovascular Diseases of Vojvodina between 2008 and 2020. In line with European Society of Cardiology guidelines, the inclusion criterion was ICD implantation following a documented episode of VF or haemodynamically unstable VT in the absence of reversible causes or acute myocardial infarction [1].

Data were collected from the hospital information system during 2021–2022 and included demographic features (age and sex); data obtained by ICD interrogation (time to first ICD-Tx, number of ICD-Tx episodes, and SCA recurrences); and clinical features, including left ventricular ejection fraction (LVEF), VF or VT as the index arrhythmia, the arrhythmogenic substrate (ischaemic cardiomyopathy [ICM], non-ischaemic cardiomyopathy [NICM], long QT syndrome, Brugada syndrome, or ARVD), the presence of heart failure with reduced LVEF (HFrEF) or heart failure with preserved LVEF (HFpEF), and the number of hospitalisations due to electrical storm.

Follow-up duration differed significantly between patients with and without SCA recurrence, owing to the wide range of implantation dates. To enable comparison between these groups, patients were further divided into two subgroups according to follow-up duration: 1 to 5 years, and longer than 5 years. Continuous variables are expressed as medians, and categorical variables as percentages. The chi-squared test was used to compare categorical variables, and the Mann–Whitney test to compare numerical variables. Cox regression analysis was used to identify independent predictors of appropriate ICD-Tx. Cumulative incidences of appropriate ICD-Tx, both for all patients and for patients with different arrhythmogenic substrates, were estimated using Kaplan–Meier curves and compared using the log-rank test. The influence of clinical features on time to first ICD-Tx, the absolute number of ICD-Tx episodes, SCA recurrences, and hospitalisations was assessed using the Kruskal–Wallis test, the Mann–Whitney test, and Spearman's rank-order correlation.

Results

During the follow-up period (median 4.46 years), 144 patients (60%) received at least one ICD-Tx. A total of approximately 3,620 ICD-Tx episodes were delivered (range 1–560). Prior sustained VT was the index arrhythmia in 60.5% of cases. Patient characteristics are shown in the first section of **Table 1**.

VT as the index arrhythmia was significantly more frequent (p=0.03) among patients who experienced SCA recurrence, in the analysis comparing subgroups followed up for 1 to 5 years. No statistically significant difference was observed in the presence of ICM, NICM, channelopathies, ARVD, HFrEF, HFpEF, or LVEF between patients with and without SCA recurrence in this subgroup (second section of **Table 1**.

Analysis of patients followed up for longer than 5 years (third section of **Table 1**) likewise showed no statistically significant difference in the presence of ICM, NICM, channelopathies, ARVD, HFrEF, HFpEF, VT as the index arrhythmia, or LVEF between patients with and without SCA recurrence.

Cox regression analysis showed that the only independent predictor of SCA recurrence was prior

Table 1. Basic patient characteristics (section 1); Chi-squared and Mann–Whitney test results (sections 2 and 3)

Demographic and clinical features	Total n=240	SCA recurrence (n=144, 60%)	No SCA recurrence (n=96, 40%)	p-value
Male sex	80.8%	81.3%	80.2%	
Age (years)	63 (20–83)	35 (18–66)	65 (32–81)	
ICM	60.9%	59%	64.6%	
NICM	32.8%	37.5%	31.3%	
Long QT, Brugada, ARVD	4.2%	5.6%	2.1%	
HFrEF	77.3%	75.7%	80.2%	
HFpEF	5%	4.9%	5.2%	
VT – index arrhythmia	60.5%	67.4%	50.5%	
LVEF	35 (18–66)	35 (18–66)	35 (18–65)	
Follow-up 1–5 years	n=126	n=63, 50%	n=63, 50%	
Male sex	83.3%	80.95%	85.71%	0.47
Age (years)	67 (22–81)	67 (22–81)	66.5 (32–81)	0.77
ICM	66.7%	58.7%	74.6%	0.06
NICM	28.6%	34.9%	22.2%	0.11
Long QT, Brugada, ARVD	4.9%	8.1%	1.6%	0.10
HFrEF	81%	74.6%	87.3%	0.07
HFpEF	4%	4.8%	3.2%	0.65
VT – index arrhythmia	61.9%	74.1%	52.4%	0.03
LVEF	35.5 (18–66)	38 (19–66)	34 (18–60)	0.10
Follow-up >5 years	n=99	n=68, 68.7%	n=31, 31.3%	
Male sex	78.8%	83.82%	67.74%	0.07
Age (years)	60 (20–76)	59.5 (20–76)	60 (35–76)	0.43
ICM	54.5%	58.8%	45.2%	0.20
NICM	42.4%	39.7%	48.4%	0.42
Long QT, Brugada, ARVD	4%	4.4%	3.2%	0.78
HFrEF	71.7%	75%	64.5%	0.28
HFpEF	7.1%	5.9%	9.7%	0.49
VT – index arrhythmia	60.6%	64.7%	48.4%	0.12
LVEF	35 (18–65)	35 (19–65)	38 (18–65)	0.63

sustained VT as the index arrhythmia (hazard ratio [HR]: 1.948, 95% confidence interval [CI]: 1.335–2.842, p=0.001). As shown in **Table 2**, these patients also had a significantly higher absolute number of ICD-Tx episodes and life-threatening arrhythmia episodes. **Table 2** further shows that patients diagnosed with channelopathy or ARVD had a significantly higher number of hospitalisations than those diagnosed with ICM or NICM. Time to first ICD-Tx did not differ significantly according to underlying cardiomyopathy, index arrhythmia, LVEF, or the presence or absence of heart failure (**Table 2**).

Cumulative incidences of ICD-Tx for all patients (**Figure 1**) and for patients with different arrhythmogenic substrates (**Figure 2**) were estimated using

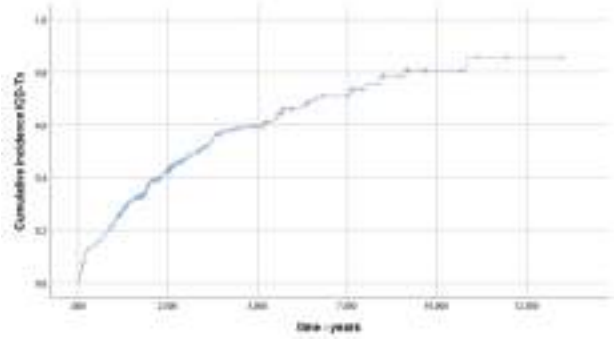

Figure 1. Cumulative incidence of ICD-Tx in all patients

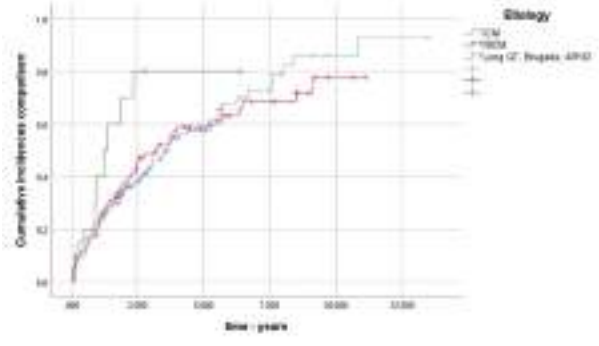

Figure 2. Cumulative incidence of ICD-Tx in patients with different arrhythmogenic substrates

Table 2. Influence of clinical features on number of hospitalisations, ICD-Tx episodes, SCA episodes, and time to first ICD-Tx (Kruskal–Wallis test, Mann–Whitney test, and Spearman's rank-order correlation results)

	Time to first ICD-Tx (months)	p-value	Number of hospitalisations	p-value
ICM	19.53 (0.03–192)	0.337	0 (0–11)	0.043
NICM	18.47 (0.23–109.2)		0 (0–5)	
Long QT, Brugada, ARVD	10.73 (1.3–34.1)		1.5 (0–6)	
HFrEF	18.78 (0.23–192)	0.469	1 (0–2)	0.631
HFpEF	34.53 (0.37–66.4)		0 (0–4)	
No HF	11.57 (0.03–109.2)		0 (0–6)	
VT	17.7 (0.03–101.6)	0.315	0 (0–11)	0.078
VF	21.87 (1–192)		0 (0–6)	
LVEF		0.560		0.476
	Number of ICD-Tx episodes	p-value	Number of SCA episodes	p-value
ICM	6 (1–560)	0.526	5 (1–547)	0.386
NICM	6 (1–150)		5 (1–150)	
Long QT, Brugada, ARVD	10 (2–328)		11 (2–324)	
HFrEF	6 (1–560)	0.725	6 (1–547)	0.607
HFpEF	7 (1–128)		6 (1–125)	
No HF	4 (1–328)		3 (1–324)	
VT	8 (1–560)	0.000	7.5 (1–547)	0.000
VF	3.5 (1–150)		3.5 (1–150)	
LVEF		0.929		0.931

Table 3. Cumulative incidence of SCA recurrence by year of follow-up

Year of follow-up – cumulative incidence (%)	Year 1	Year 2	Year 5	Year 10
All patients	23.2	38.1	59.3	80.7
ICM	22.2	35.6	57.6	85.9
NICM	20	38.2	61	77.5
Long QT, Brugada, ARVD	40	70	80	80
Patients at risk for the period	n=236	n=182	n=63	n=11

Kaplan–Meier curves. The log-rank test showed no statistically significant difference in cumulative incidence of SCA recurrence between patients with ICM, NICM, and ARVD/channelopathies. Cumulative incidences of SCA recurrence are shown in **Table 3**.

Discussion

AVID, CASH, and CIDS are randomised clinical trials that have shown the superiority of ICD implantation for secondary prevention, reducing overall and arrhythmic mortality by 28% and 50% respectively, compared with antiarrhythmic drug therapy alone [12–14]. Borleffs et al. studied 456 patients with an ICD implanted for secondary prevention of SCD in a prospective study with a mean follow-up of 4.5 years, reporting five-year and ten-year cumulative incidences of ICD-Tx of 52% and 61% respectively [15]; similar results were obtained in the retrospective study by Schaer et al., which included 357 patients with a mean follow-up of 6.83 years and five-year and ten-year cumulative incidences of 59.2% and 65.3% [16]. The five-year cumulative incidence of 59.3% in our study was comparable to the findings reported by others. In contrast, our ten-year cumulative incidence was higher at 80.7%, possibly reflecting the smaller number of patients followed beyond 10 years. Lower values were reported in a retrospective Japanese study, in which Nagahara et al. found one-year, three-year, and five-year ICD-Tx rates of 32%, 49%, and 46% respectively [17]. Takano et al. conducted a prospective study with a mean follow-up of 2.4 years, including 96 patients with ICM, in which one-year, three-year, and five-year cumulative incidences of ICD-Tx were 26%, 53.1%, and 64.6% respectively [18] – similar to our patients with ICM, in whom the corresponding values were 22.2%, 47%, and 57.6%.

Schaer et al. identified age (HR: 1.024, 95% CI: 1.010–1.038, p=0.001) and VT as the presenting arrhythmia (HR: 1.450, 95% CI: 1.047–2.008, p=0.025) as independent predictors of SCA recurrence [16]. Borleffs et al. identified atrial fibrillation or flutter, VT presentation (HR: 1.51, 95% CI: 1.05–2.18), a

wider QRS complex, and lower LVEF as independent predictors, with atrial fibrillation the strongest predictor (HR: 2.1, 95% CI: 1.3–3.2) [15]. In a prospective study restricted to patients with ICM, Takano et al. identified higher creatinine levels (HR: 1.294, 95% CI: 1.020–1.641, p=0.034), lower LVEF (HR: 3.713, 95% CI: 1.920–7.180, p<0.001), and incomplete revascularisation (HR: 2.406, 95% CI: 1.179–4.910, p=0.016) as independent predictors of appropriate ICD-Tx [18]. Nagahara et al. found that persistent VT as the cause of implantation was the only independent predictor of SCA recurrence (HR: 2.80, 95% CI: 1.60–4.46, p=0.001) [17], consistent with our findings (HR: 1.948, 95% CI: 1.335–2.842, p=0.001). A comparable result was obtained in the AVID randomised clinical trial in 1997, in which Klein et al. found a significantly higher cumulative incidence of ICD-Tx in patients whose ICD was implanted following an episode of VT (p=0.001) than in those whose index arrhythmia was VF [14]. It remains unclear why recurrence rates differ according to index arrhythmia; one possible explanation is the stability of the reentry circuit substrate characteristic of monomorphic VT, which allows greater reproducibility of ventricular arrhythmias of sufficient duration to trigger appropriate ICD-Tx [17].

Whether the risk of SCA recurrence varies with the underlying aetiology of ventricular arrhythmia also remains unclear. Nagahara et al.'s study included 50 patients with ICM, 15 with non-ischaemic dilated cardiomyopathy (NIDCM), 33 with HCM, 10 with ARVD, 16 with cardiac sarcoidosis, and 11 with valvular heart disease. They found no significant difference in aetiology between patients with and without SCA recurrence [17]. Dharma et al. compared the incidence of appropriate ICD-Tx between patients with ICM and NICM in a study in which 26% of patients had an ICD implanted for secondary prevention, finding comparable incidences over a mean follow-up of 19 months [19]. Our results are consistent with these studies, with no significant difference observed in the cumulative incidence of SCA recurrence across different arrhythmia aetiologies.

These findings support the utility of ICDs in preventing SCD, regardless of quality-of-life considerations or long-term patient acceptance of the device [20,21].

Conclusion

The incidence of implantable cardioverter defibrillator therapy delivery is high among patients treated for secondary prevention of sudden cardiac death, regardless of aetiology. Prior sustained ventricular tachycardia as the indication for implantable cardioverter defibrillator implantation predicted a higher incidence and absolute number of appropriate defibrillator therapies. Various studies have sought to identify predictors of sudden cardiac arrest recurrence following defibrillator implantation for secondary prevention of sudden cardiac death; however, no reliable predictor has yet been identified.

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