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Factors predisposing to ventricular tachyarrhythmia leading to appropriate ICD intervention in patients with coronary artery disease or non-ischaemic dilated cardiomyopathy

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Abstract

Background: In order to achieve optimal outcomes when treating ventricular tachyarrhythmias with implantable devices, it is extremely important to identify parameters predisposing to arrhythmia. In view of current restrictions in healthcare funding, there is a growing demand for additional predictors of arrhythmia that would allow better patient selection for implantable cardioverter-defibrillator (ICD) use for primary prevention of sudden cardiac death (SCD).

Aim: To identify parameters predisposing to ventricular tachyarrhythmia/appropriate ICD intervention in ICD recipients.

Methods: We analysed 376 patients (56 women, 320 men, mean age 66.1 ± 11.2 [range 22–89] years) who underwent ICD implantation between January 2008 and December 2010. Of these, 275 patients underwent ICD implantation for primary prevention of SCD and 101 for secondary prevention. Operative protocols and in-hospital and outpatient records were analysed retrospectively. Mean QRS width and heart rate (HR) were calculated in resting surface electrocardiograms (25 mm/s, 10 mm/1 mV). Intracardiac electrograms stored in ICD memory were used to evaluate appropriateness of anti-arrhythmic interventions and analyse the number of ventricular tachyarrhythmia events, ICD interventions and their type. We analysed the following clinical and procedural variables: age, gender, left ventricular ejection fraction (LVEF), type of SCD prevention (primary or secondary), ICD type (single chamber — VR, dual chamber — DR), performing defibrillation threshold testing to establish defibrillation safety margin at ICD implantation, ventricular lead location (right ventricular outflow tract region, right ventricular apex), mean HR, QRS width, New York Heart Association (NYHA) functional class, occurrence of ventricular tachyarrhythmia/appropriate ICD intervention after implantation, ICD interventions, history of cardiovascular disease and arrhythmia (myocardial infarction, ischaemic and non-ischaemic dilated cardiomyopathy, arterial hypertension, ventricular fibrillation, ventricular tachycardia, permanent atrial fibrillation, percutaneous coronary intervention, and/or coronary artery bypass grafting), and medications (amiodarone, sotalol, beta-blockers, angiotensin-converting enzyme inhibitors [ACEI]/angiotensin receptor blockers [ARB], statins, loop diuretics, aldosterone antagonists).

Results: During the mean follow-up period of 387 ± 300 (range 5–1400) days, appropriate ICD intervention due to ventricular tachyarrhythmia occurred in 68 of 376 ICD patients (61 men, 7 women, mean age 64.7 ± 12.3 [range 22–89] years). Mean time interval from ICD implantation to the occurrence of arrhythmia was 281 ± 229 (range 5–972) days (p < 0.001). To optimize sensitivity and specificity when analysing ventricular tachyarrhythmia/appropriate ICD intervention vs. no ventricular tachyarrhythmia/appropriate ICD intervention, cutoff values were established using ROC curves (cutoff for LVEF = = 31%, HR = 79 bpm). Using these cutoff values, patients with ventricular tachyarrhythmia/appropriate ICD intervention were compared to those without ventricular tachyarrhythmia/appropriate ICD intervention. Significant differences were observed in LVEF (p < 0.001), HR (p < 0.022), ACEI/ARB use (p < 0.034), and NYHA class (p < 0.001). By Kaplan-Meier

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univariate analysis, patients with LVEF > 31% (log-rank test p < 0.001), HR ≤ 79 bpm (log-rank test p < 0.022), QRS width ≤ 114 ms (log-rank test p < 0.045), and NYHA class II (log-rank test p < 0.001) were more likely to be free from ventricular tachyarrhythmia/appropriate ICD intervention. Cox multivariate analysis showed that reduced LVEF (≤ 31%) was the only independent predictor of arrhythmia/intervention. LVEF values below 31% are associated with a significant 20-fold increase (p < 0.02) in the risk of arrhythmia during the first 3 years after ICD implantation. Among 68 patients with ventricular tachyarrhythmia/appropriate ICD intervention, mean 4.1 interventions per person occurred during the follow-up period. In the overall study population, the number of interventions was 0.28 per person per year. Overall, 92 inappropriate ICD interventions were observed, all resulting from atrial fibrillation with rapid ventricular rate. Interventions had no effect on total mortality. Higher numbers of appropriate interventions were observed in patients who died due to heart failure.

Conclusions: Factors associated with a significantly increased risk of ventricular tachyarrhythmia/appropriate ICD intervention included reduced LVEF, increased resting HR, NYHA class II or higher heart failure, and wide QRS. Patients with low LVEF (< 31%) are at particular risk of SCD due to ventricular arrhythmia and this parameter alone can influence the decision regarding ICD implantation. No effect of ICD interventions on total mortality was observed, although more ICD interventions were observed in patients who died due to heart failure.

Key words: implantable cardioverter-defibrillator (ICD), predictors of ventricular tachyarrhythmia, ICD intervention

INTRODUCTION

Implantable cardioverter-defibrillator (ICD) may terminate ventricular tachyarrhythmia, including ventricular tachycardia (VT), fast ventricular tachycardia (FVT), and ventricular fibrillation (VF), by low-voltage antitachycardia pacing (ATP) or high-energy cardioversion (CV) [1, 2].

The purpose of ICD implantation is to prevent sudden cardiac death (SCD) due to VF or VT, and terminate VT events that might load to haemodynamic compromise. Randomised multicentre trials showed effectiveness of this treatment both in patients after a VT/VF episode (secondary prevention) and in high-risk primary prevention patients.

Of note, however, inappropriate ICD interventions may significantly reduce quality of life, or even be associated with an increased mortality risk [3]. Statistically significant predictors of inappropriate ICD interventions in the MADIT II study included atrial fibrillation (AF), smoking, and diastolic blood pressure > 80 mm Hg. Inappropriate high-energy interventions in the treatment of an initial tachyarrhythmia episode in the AVID occurred in 24% of patients [4]. Causes include atrial tachyarrhythmias with rapid ventricular rate (AF, supraventricular tachycardia, sinus tachycardia), abnormal ICD sensing (e.g., atrial pacing sensed in ventricular channel, R and/or T wave oversensing, diaphragmatic or other myopotential oversensing), ICD failure, and electromechanical interference.

Optimal management of these patients heavily relies on ICD Holter memory which is a routine feature of currently used devices. Data stored include intracardiac electrogram recorded immediately prior to tachyarrhythmia detection (usually over several seconds), R-R intervals (recorded over a relatively longer period compared to electrogram), interventions and their outcomes, and electrical parameters (lead impedance, defibrillating impulse voltage, charging time). ICD Holter memory is mainly used to evaluate appropriateness of arrhythmia detection, particularly in patients with concomitant supraventricular tachyarrhythmias. It may also be used to evaluate ICD status, as impedance changes were shown to be a sensitive indicator of lead damage, and prolonged charging time indicates low battery [5].

In order to achieve optimal outcomes when treating ventricular tachyarrhythmias with implantable devices, it is extremely important to identify parameters predisposing to arrhythmia as they may indicate which patients are most likely to benefit from ICD implantation. In the current era of prophylactic ICD therapy and restrictions in healthcare funding, identification of such additional predictors of ventricular tachyarrhythmia would allow better patient selection.

The aim of the study was to identify parameters predisposing to ventricular tachyarrhythmia and subsequent appropriate ICD intervention in ICD recipients.

METHODS
Study population

Between January 2008 and December 2010, an ICD without cardiac resynchronisation therapy capability was implanted in 376 patients (56 females, 320 males, mean age 66.1 ± ± 11.2 [range 22–89] years). Of these, 275 patients underwent ICD implantation for primary prevention of SCD and 101 for secondary prevention. Study group characteristics are shown in Tables 1A, B.

Inclusion criteria were as follows:
— coronary artery disease (CAD), previous myocardial infarction (MI), ischaemic (IDCM) or non-ischaemic dilated cardiomyopathy (NIDCM), with ICD implanted for primary or secondary prevention of SCD;
— complete in-hospital and outpatient records (at least 3 follow-up visits at an ICD clinic, with printed device

Table 1A. Study group characteristics and ICD interventions

Parameter	N	%	Mean	SD	Median	Min	Max	Overall
Age [years]	376	100.0	66.1	11.21	66	22	89	
Ejection fraction [%]	376	100.0	34.28	6.44	35	12	65	
Heart rate [bpm]	376	100.0	74.56	8.12	76	62	106	
QRS width [ms]	376	100.0	110.52	10.35	112	86	160	
Number of appropriate interventions	68	18.1	4.1	9.7	2	1	60	282
Number of unsuccessful interventions	8	2.1	1.9	1.6	1	1	5	15
Self-terminating VT and/or VF	54	14.4	1.1	0.4	1	1	3	60
Number of inappropriate CV interventions	31	8.2	3	2.3	2	1	11	92
Number of appropriate ATP interventions	50	13.3	4.5	11.1	2	1	57	227
Number of appropriate CV interventions	35	9.3	1.6	0.9	1	1	4	55

No intervention = self-terminating VT and/or VF; VT — ventricular tachycardia; VF — ventricular fibrillation; CV — cardioversion; ATP — antitachycardia pacing

Table 1B. Study group characteristics — gender, type of prevention, ICD type, technical parameters, history of cardio-vascular disease, arrhythmia and revascularization, NYHA class, medications, mortality

Female gender	56 (14.9%)
Male gender	320 (85.1%)
Primary prevention	275 (73.1%)
Secondary prevention	101 (26.9%)
ICD DR	161 (42.8%)
ICD VR	215 (57.2%)
Lead located in RVOT	253 (67.3%)
Lead located at RV apex	123 (32.7%)
DFT at ICD implantation	182 (48.4%)
Previous myocardial infarction	206 (54.8%)
Dilated cardiomyopathy (DCM, ICM)	333 (88.6%)
Arterial hypertension	119 (31.6%)
Ventricular fibrillation	61 (16.2%)
Sustained or non-sustained VT	217 (57.7%)
Chronic atrial fibrillation	102 (27.1%)
Previous PCI	89 (23.7%)
Previous CABG	42 (11.2%)
NYHA class II	85 (22.6%)
NYHA class III	228 (60.6%)
NYHA class IV	63 (16.8%)
Amiodarone	73 (19.4%)
Sotalol	14 (3.7%)
Beta-blocker	331 (88%)
ACEI/ARB	283 (75.3%)
Statin	264 (70.2%)
Loop diuretic	236 (62.8%)
Aldosterone antagonist	257 (68.4%)
Deaths overall	46 (12.2%)
Sudden death	16 (4.3%)
Other causes of death	10 (2.7%)
Death due to heart failure	20 (5.3%)
Overall number of patients	376 (100.0%)

ACEI — angiotensin-converting enzyme inhibitor; ARB — angiotensin receptor blockers; CABG — coronary artery bypass grafting; DCM — dilated cardiomiopathy; DFT — defibrillation threshold testing; ICM — ischaemic cardiomiopathy; ICD — implantable cardioverter-defibrillator; NYHA — New York Heart Association; PCI — percutaneous coronary intervention; RV — right ventricle; RVOT — right ventricular outflow tract; VT — ventricular tachycardia

interrogation reports and resting electrocardiograms [ECGs]).
— regular patient contact with the ICD clinic.
Exclusion criteria included:
— aetiology other than CAD and NIDCM (e.g., arrhythmia related to genetic causes, cardiac arrest of unknown cause);
— complete pacemaker dependence (100% of paced beats, no intrinsic cardiac beats);
— incomplete in-hospital and outpatient records;
— loss of patient contact with the ICD clinic.

Study variables

ICD implantation protocols and in-hospital and outpatient records were reviewed retrospectively. Follow-up clinic visits were performed on average every 3 months. Goals of follow-up clinic visits included evaluation of the health status of the patient, ICD parameters, appropriateness of ICD interventions, and drug therapy used, as well as answering patient questions regarding treatment, daily life activities and professional work. Battery status, capacitor charging time, pacing thresholds, amplitude of intrinsic cardiac beats, and lead resistance were routinely assessed during each follow-up visit. We analysed resting ECGs at 25 mm/s and 10 mm/1 mV to calculate average intrinsic QRS width and resting heart rate (HR), and intracardiac electrograms stored in the ICD memory to evaluate appropriateness of antiarrhythmic interventions. In case of chronic AF, a mean of 2 shortest and longest RR intervals was calculated, and mean HR was calculated [6]. HR was analysed collectively for sinus rhythm and AF. For calculations, mean values from each follow-up visit were taken, and an overall mean value for all follow-up visits was given at the end of follow-up.

We analysed the following clinical and technical variables: gender, age, left ventricular ejection fraction (LVEF), type of SCD prevention (primary or secondary), ICD type (single chamber — VR, dual chamber — DR), performing defibrillation threshold testing (DFT) to establish defibrillation safety

margin at ICD implantation, ventricular lead location (right ventricular outflow tract [RVOT] region, right ventricular [RV] apex), HR, QRS width, New York Heart Association (NYHA) functional class, occurrence of ventricular tachyarrhythmia episode leading to appropriate ICD intervention, history of cardiovascular disease and arrhythmia (previous MI, IDCM and NIDCM, arterial hypertension, previous VF, sustained or non-sustained VT, chronic AF, previous percutaneous coronary intervention [PCI] and/or coronary artery bypass grafting [CABG]), and medications used (amiodarone, sotalol, beta--blockers, angiotensin-converting enzyme inhibitors [ACEI]//angiotensin receptor blockers [ARB], statins, loop diuretics, aldosterone antagonists). Data regarding risk factors were derived from the hospital discharge summary after ICD implantation, and data regarding medications, QRS width, HR, and number and types of ICD intervention were collected throughout follow-up. Appropriateness of the ventricular lead location was not verified.

We evaluated the number of ventricular tachyarrhythmia events (detected in VT, VF, and FVT zones), appropriate ICD interventions and their types (ATP, CV), inappropriate ICD interventions, unsuccessful first programmed interventions, and self-terminating VT and VF episodes without ICD intervention.

Appropriate ICD intervention was defined as ICD therapy (ATP and/or CV) due to appropriately detected ventricular tachyarrhythmia (VT or VF).

The study endpoint was the occurrence of a ventricular tachyarrhythmia event (detected in a VT, VF or FVT zone) with a rate above 162 bpm, leading to appropriate ICD intervention (ATP and/or CV). Ventricular tachyarrhythmias with a lower ventricular rate were not included. Inappropriate interventions, unsuccessful first programmed interventions, and self-terminating VT and VF episodes without ICD intervention did not constitute an endpoint. Patients with such interventions were included into the group with no ventricular tachyarrhythmia/appropriate ICD intervention (i.e., no endpoint occurrence). Follow-up was terminated with patient death. If a patient died without prior ventricular tachyarrhythmia event leading to appropriate ICD intervention, he was included into the group with no endpoint occurrence. This group also included patients with no ventricular tachyarrhythmia and no intervention.

The VT detection zone was programmed in the range of 162–200 bpm (R-R interval 370–300 ms), and the VF zone above 200 bpm (R-R interval < 300 ms). If available, the FVT detection zone was also programmed in selected ICD models in the range of 200–240 bpm (R-R interval 300–250 ms).

In the VT detection zone, ATP was always the initial therapy, followed by high-energy CV if unsuccessful. In the VF detection zone, high-energy therapy was programmed as the initial therapy (35 or 40 J depending on the ICD model). The option of "ATP during charging", available in modern ICDs, was also used in the VF detection zone. Of note, arrhythmia detection algori-

thms could not be completely standardised due to different therapeutic approaches used by different ICD manufacturers. Arrhythmia differentiation criteria were switched on.

The protocol of this follow-up study was approved by a local ethics committee (Komisja Bioetyczna, Okręgowa Izba Lekarska, Kraków).

Statistical analysis

Descriptive parameters of quantitative variables included arithmetic mean ± standard deviation (SD), median, maximum and minimum value, and sample size (*n*). Differences in quantitative variables between groups were tested using the Student t test for independent samples or the Mann-Whitney test, depending on the variable distribution. Descriptive parameters of qualitative variables included numbers and percentages of answers "yes" and "no" for a given category (*n*, N_1, N_2) as shown in contingency tables. Differences in qualitative variables between groups were tested using the χ^2 test or the exact Fisher test. Receiver operating characteristic (ROC) curves were plotted to obtain cutoff values of quantitative variables providing optimal sensitivity and specificity of a given diagnostic parameter for ventricular tachyarrhythmia leading to appropriate ICD intervention. Kaplan-Meier survival curves were used to evaluate survival free from ventricular tachyarrhythmia and appropriate ICD intervention depending on the value of a specific dichotomous variable. Significance of the differences between survival curves for the 2 categories of a given dichotomous variable was tested using the long rank test (univariate analysis). Based on the univariate analyses, variables with a significant effect on the occurrence of ventricular tachyarrhythmia leading to appropriate ICD intervention were identified and included stepwise into a multivariate Cox proportional hazard model. Model parameters were calculated using Breslow approximation of the partial likelihood function. During each step, a variable with the highest p value for the Wald statistics was removed from the full model by stepwise elimination, provided that the p value was > 0.05. After the last step, only variables with a significant effect on the occurrence of first ventricular tachyarrhythmia leading to appropriate ICD intervention remained in the model (p ≤ 0.05). Multivariate analysis of quantitative variables was also included in the statistical analysis. Statistical hypotheses were verified at $\alpha = 0.05$. Calculations were performed using the STATISTICA 9.0 PL package (StatSoft, Inc.), MedCalc v. 10.4.3.0., and MS Office Excel.

RESULTS

During the mean follow-up period of 387 ± 300 days (range 5–1400 days), appropriate ICD intervention due to ventricular tachyarrhythmia occurred in 68 of 376 ICD patients (61 men, 7 women, mean age 64.7 ± 12.3 [range 22–89] years). The remaining 308 patients (259 men, 49 women, mean age 67.1 ± 10.2 [range 23–88] years) without tachyarrhythmia/

/appropriate ICD intervention had self-terminating VT and VF episodes without ICD intervention, inappropriate and unsuccessful ICD interventions, or no ventricular tachyarrhythmia. Mean time interval from ICD implantation to the occurrence of arrhythmia was 281 ± 229 (range 5–972) days, p < 0.001. To optimize sensitivity and specificity of a given diagnostic parameter when analysing ventricular tachyarrhythmia/appropriate ICD intervention vs. no ventricular tachyarrhythmia/ /appropriate ICD intervention, optimal cutoff values were established using ROC curves. Among analysed parameters, including age (cutoff 68 years), QRS width (114 ms), HR (79 bpm), and LVEF (31%), significant results were obtained for HR (p < 0.042) and LVEF (p < 0.001) (Figs. 1, 2). Using these

cutoff values, patients with ventricular tachyarrhythmia/appropriate ICD intervention were compared to those without ventricular tachyarrhythmia/appropriate ICD intervention (Tables 2A, B, C). Significant differences were observed in LVEF (p < 0.001), HR (p < 0.022), NYHA class (p < 0.001), and ACEI/ARB use (p < 0.034). Parameters from Tables 2A, B, C, at p ≤ 0.23, were then analysed using the Kaplan-Meier method. In univariate analyses, significant predictors of survival free from ventricular tachyarrhythmia/appropriate ICD intervention were LVEF > 31% (log-rank test p < 0.001), HR ≤ 79 bpm (log-rank test p < 0.022), QRS width ≤ 114 ms (log-rank test p < 0.045), and NYHA class II (log-rank test p < 0.001) (Fig. 3).
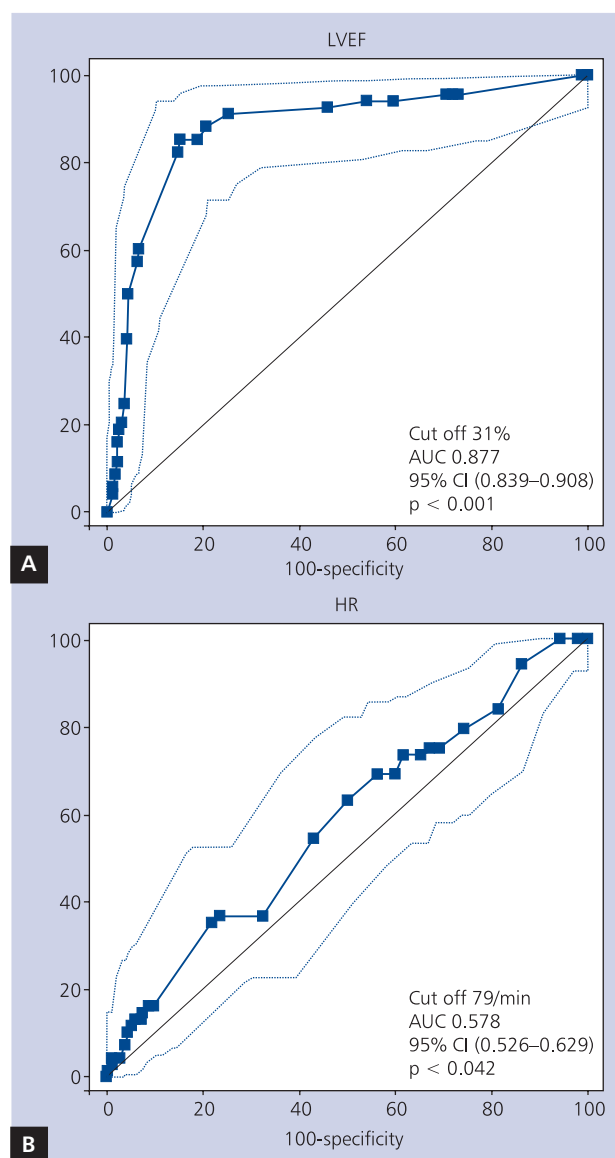

Figure 1. Receiver operating characteristic curves to optimize sensitivity and specificity of a given diagnostic parameter: left ventricular ejection fraction (LVEF) (**A**), mean resting heart rate (HR) (**B**)
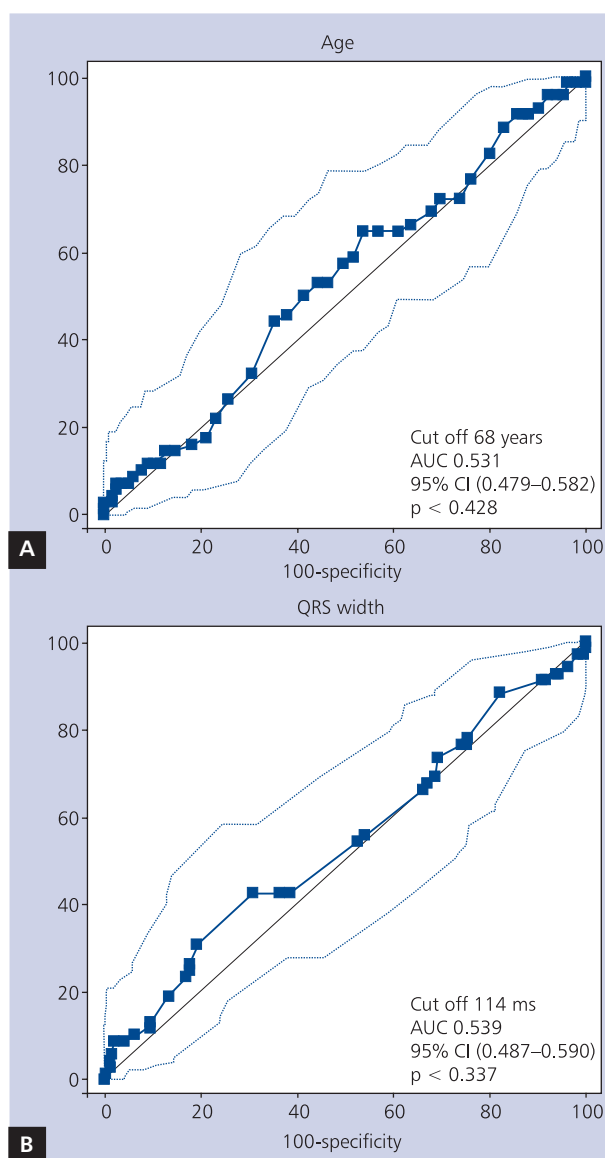
Figure 2. Receiver operating characteristic curves to optimize sensitivity and specificity of a given diagnostic parameter: age (**A**), mean QRS width (**B**)

Table 2A. Differences in the evaluated parameters between patients with or without ventricular tachyarrhythmia/appropriate ICD intervention

Parameters	Arrhythmia		No arrhythmia		Overall		P
	N₁	%	N₂	%	n	%	
Gender							
Female	7	10.3	49	15.9	56	14.9	0.239
Male	61	89.7	259	84.1	320	85.1	
Age* [years]							
≤ 68	44	64.7	166	53.9	210	55.9	0.104
> 68	24	35.3	142	46.1	166	44.1	
Prevention							
Primary	48	70.6	227	73.7	275	73.1	0.600
Secondary	20	29.4	81	26.3	101	26.9	
ICD type							
DR	27	39.7	134	43.5	161	42.8	0.566
VR	41	60.3	174	56.5	215	57.2	
DFT							
Yes	39	57.4	143	46.4	182	48.4	0.103
No	29	42.6	165	53.6	194	51.6	
Lead location							
RVOT	45	66.2	208	67.5	253	67.3	0.829
RV apex	23	33.8	100	32.5	123	32.7	
EF* [%]							
≤ 31	58	85.3	47	15.3	105	27.9	**< 0.001**
> 31	10	14.7	261	84.7	271	72.1	
HR* [bpm]							
≤ 79	44	64.7	240	77.9	284	75.5	**0.022**
> 79	24	35.3	68	22.1	92	24.5	
QRS width* [ms]							
≤ 114	39	57.4	212	68.8	251	66.8	0.069
> 114	29	42.6	96	31.2	125	33.2	
NYHA class							
II	4	5.9	81	26.3	85	22.6	
III	24	35.3	204	66.2	228	60.6	**< 0.001**
IV	40	58.8	23	7.5	63	16.8	

*Cutoff values for optimal sensitivity and specificity in the prediction of ventricular tachyarrhythmia resulting in appropriate ICD intervention identified using receiver operating characteristics (ROC) curves; Arrhythmia = ventricular tachyarrhythmia resulting in appropriate ICD intervention. No arrhythmia = no ventricular tachyarrhythmia resulting in appropriate ICD intervention; DFT — defibrillation threshold testing; EF — ejection fraction; HR — heart rate; ICD — implantable cardioverter-defibrillator; NYHA — New York Heart Association; RV — right ventricle; RVOT — right ventricular outflow tract

Cox multivariate analysis showed that reduced LVEF (≤ 31%) was the only independent predictor of ventricular tachyarrhythmia/appropriate ICD intervention (regression coefficient 1.49, p < 0.01, hazard ratio [HR] 19.7, 95% confidence interval [CI] 10–38.7). LVEF values below 31% are associated with a significant 20-fold increase in the risk of ventricular tachyarrhythmia/appropriate ICD intervention during the first 3 years after ICD implantation, as shown in Figure 4. The remaining variables (age, gender, type of prevention, ICD type, DFT performance, ventricular lead location, mortality, cause of death, history of cardiovascular disease and arrhythmia, and medications used) were not identified as significant predictors of ventricular tachyarrhythmia/appropriate ICD intervention. These results were also confirmed in multivariate analysis of quantitative variables.

Among 68 patients with ventricular tachyarrhythmia/appropriate ICD intervention, 227 appropriate ATP events and 5 appropriate CV events were recorded in the VT detection zone, and 50 appropriate CV events were recorded in the VF detection zone. Among these patients, mean 4.1 interven-

Table 2B. Differences in the rates of cardiovascular disease, arrhythmia and revascularisation between patients with or without ventricular tachyarrhythmia/appropriate ICD intervention

Cardiovascular disease and arrhythmia	Arrhythmia		No arrhythmia		Overall		P
	N_1	%	N_2	%	n	%	
Previous myocardial infarction	41	60.3	165	53.6	206	54.8	0.313
Dilated cardiomyopathy (DCM and ICM)	57	83.8	276	89.6	333	88.6	0.175
Arterial hypertension	24	35.3	95	30.8	119	31.6	0.475
Ventricular fibrillation	13	19.1	48	15.6	61	16.2	0.474
Sustained and non-sustained ventricular tachycardia	37	54.4	180	58.4	217	57.7	0.543
Chronic atrial fibrillation	17	25.0	85	27.6	102	27.1	0.663
Previous PCI	16	23.5	73	23.7	89	23.7	0.976
Previous CABG	6	8.8	36	11.7	42	11.2	0.497
Overall	68	100.0	308	100.0	376	100.0	–

Arrhythmia = ventricular tachyarrhythmia resulting in appropriate ICD intervention; No arrhythmia = no ventricular tachyarrhythmia resulting in appropriate ICD intervention; CABG — coronary artery bypass grafting; DCM — dilated cardiomiopathy; ICM — ischaemic cardiomiopathy; PCI — percutaneous coronary intervention

Table 2C. Differences in drug therapy between patients with or without ventricular tachyarrhythmia/appropriate ICD intervention

Drug	Arrhythmia		No arrhythmia		Overall		P
	N_1	%	N_2	%	n	%	
Amiodarone	13	19.1	60	19.5	73	19.4	0.945
Sotalol	3	4.4	11	3.6	14	3.7	0.740
Beta-blocker	64	94.1	267	86.7	331	88.0	0.088
ACEI/ARB	58	85.3	225	73.1	283	75.3	**0.034**
Statin	47	69.1	217	70.5	264	70.2	0.827
Loop diuretic	47	69.1	189	61.4	236	62.8	0.231
Aldosterone antagonist	49	72.1	208	67.5	257	68.4	0.468
Overall	68	100.0	308	100.0	376	100.0	–

Arrhythmia = ventricular tachyarrhythmia resulting in appropriate ICD intervention; No arrhythmia = no ventricular tachyarrhythmia resulting in appropriate ICD intervention; ACEI — angiotensin-converting enzyme inhibitor; ARB — angiotensin receptor antagonist

tions per person occurred during the follow-up period. In the overall study population, the number of interventions was 0.28 per person per year.

The rate of appropriate ICD interventions was 20% in primary prevention and 17% in secondary prevention.

Overall, 92 inappropriate ICD interventions were observed, all resulting from AF with rapid ventricular rate. In another 8 cases, 15 ATP interventions (burst) were unsuccessful as first programmed interventions (Table 1A).

When the numbers of inappropriate and appropriate ICD interventions were analysed depending on the ICD type (VR vs. DR), we found that inappropriate interventions were significantly more common in patients with ICD VR (80.6% vs. 19.4%, p < 0.05).

Interventions had no effect on total mortality (Table 3A), but a higher rate of appropriate interventions was observed in patients who died due to heart failure (HF) (Table 3B).

DISCUSSION

Among our patients with IDCM or NIDCM, in whom ICD was implanted for primary or secondary prevention of SCD, predictors of ventricular tachyarrhythmia/appropriate ICD intervention included reduced LVEF (≤ 31%), increased resting HR (> 79 bpm), wide QRS (> 114 ms), and NYHA class II or higher HF. The most important predictor of malignant ventricular arrhythmia is LV dysfunction and remodelling following MI, leading to ventricular dilatation and HF. Reduced LVEF is a major criterion in the selection of patients for ICD implantation for primary prevention, as highlighted in the 2008 ACC/AHA/HRS guidelines. In addition, LVEF was the only common inclusion criterion in all clinical trials on ICD. Arrhythmic death is most common in NYHA class II/III. With LVEF in the range of 30––40%, additional risk factors of SCD should be also taken into account. NYHA class IV patients with a very low LVEF
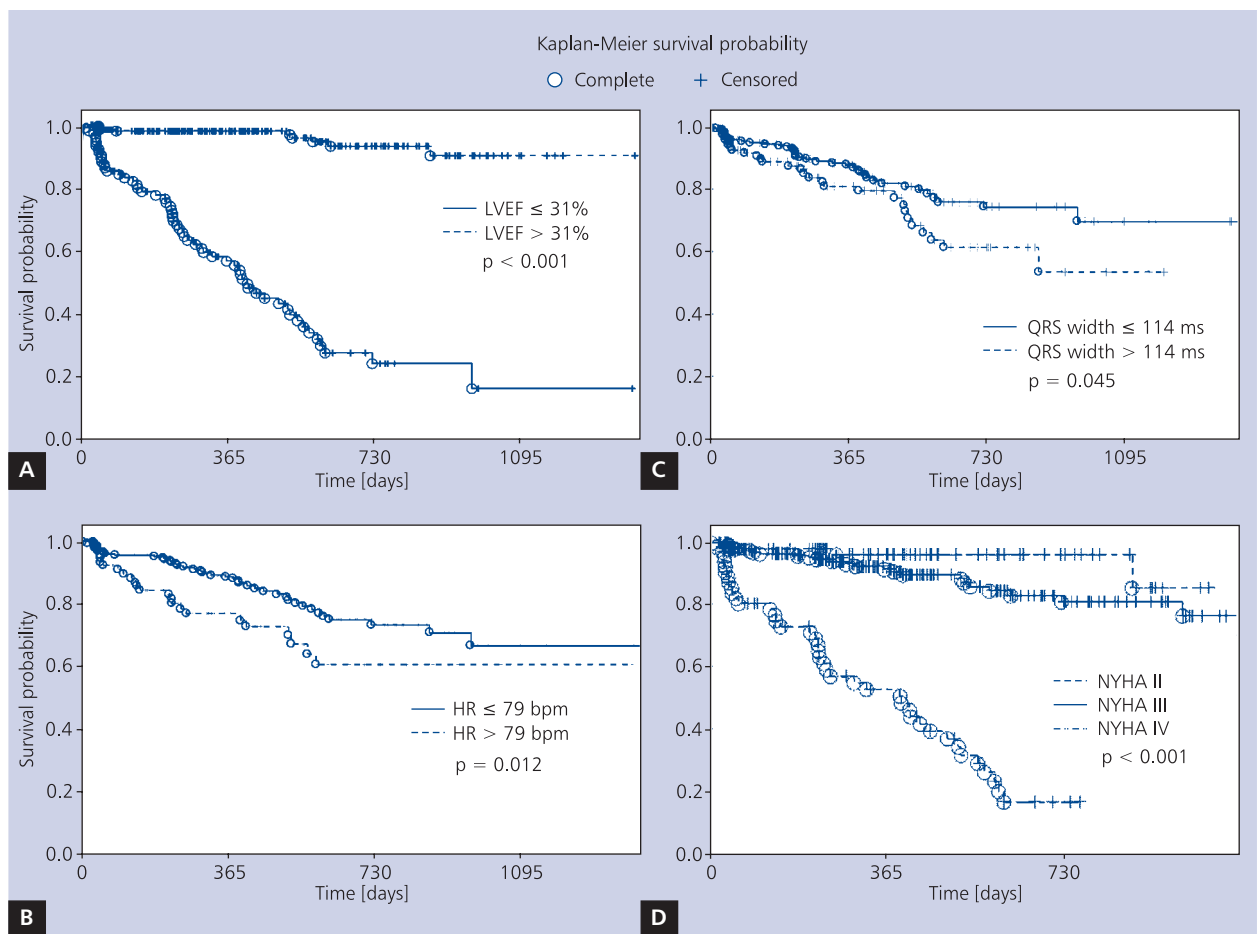
Figure 3. Kaplan-Meier curves for the probability of survival free from ventricular tachyarrhythmia/appropriate ICD intervention depending on left ventricular ejection fraction (LVEF) (**A**), mean resting heart rate (HR) (**B**), mean QRS width (**C**), and New York Heart Association (NYHA) class (**D**)

(< 15–20%) may be poor candidates for ICD implantation, as arrhythmia is not a predominant cause of death among these patients [7]. The exception may be implantation of an ICD, particularly a device with cardiac resynchronisation capability (CRT-D), in patients awaiting heart transplantation. In our study population with ischaemic heart disease and NIDCM, LVEF ≤ 31% was the only significant predictor of ventricular tachyarrhythmia/appropriate ICD intervention in the multivariate analysis. Similar findings have been reported by other authors. In the Prospective Analysis of Risk Factor for Appropriate ICD Therapy (PROFIT) study, LVEF < 40%, NT-proBNP level ≥ 405 ng/L, QRS width ≥ 150 ms, presence of AF, and higher NYHA class were associated with the occurrence of ventricular arrhythmia following ICD implantation, and the only independent predictors in multivariate Cox regression analysis included LVEF, QRS width, and AF [8]. Similar conclusions were reached by Budeus et al. [9] who also
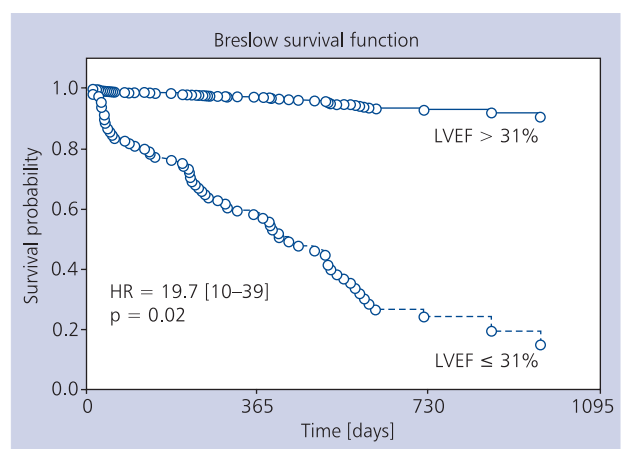

Figure 4. Probability of ventricular tachyarrhythmia/appropriate ICD intervention estimated using a Cox regression model in patients with left ventricular ejection fraction (LVEF) ≤ 31% (dashed line) and patients with LVEF > 31% (solid line)

Table 3A. Differences in drug therapy between patients with or without ventricular tachyarrhythmia/appropriate ICD intervention

Type of intervention	Non-survivors		Survivors		Overall		P
	n	%	n	%	n	%	
Appropriate intervention	10	21.7	58	17.6	68	18.1	0.492
Inappropriate intervention	6	13.0	25	7.6	31	8.2	0.206
Appropriate and inappropriate interventions overall	15	32.6	80	24.2	95	25.3	0.221
No intervention	2	4.3	52	15.8	54	14.4	**0.042**
Total	46	100.0	330	100.0	376	100.0	–

No intervention = self-terminating ventricular tachycardia and/or ventricular fibrillation

Table 3B. Types of ICD interventions in patients who died due to heart failure (HF) versus the remaining patients

Type of intervention	Remaining patients		Death due to HF		Overall		P
	n	%	n	%	n	%	
No intervention	53	14.9	1	5.0	54	14.4	0.331
Inappropriate intervention	28	7.9	3	15.0	31	8.2	0.221
Appropriate intervention	61	17.1	7	35.0	68	18.1	**0.043**
Appropriate and inappropriate interventions overall	86	24.2	9	45.0	95	25.3	**0.038**
Total	356	100.0	20	100.0	376	100.0	–

No intervention = self-terminating ventricular tachycardia and/or ventricular fibrillation

showed usefulness of electrophysiological studies for predicting late ventricular tachyarrhythmias. In contrast, Buxton et al. [10] were unable to show usefulness of QRS width in predicting ventricular tachyarrhythmia following ICD implantation. Daubert et al. [11] confirmed usefulness of programmed ventricular stimulation before ICD implantation in predicting VT but not VF in ICD patients. On the other hand, Rinaldi et al. [12] concluded that a positive result of programmed ventricular stimulation does not predict high-energy therapy in patients with dilated cardiomyopathy. Thus, previous results have not been consistent, and our findings are in concordance with studies by Dehghani et al. [13] who confirmed that QRS width and LVEF are predictors of ventricular arrhythmia, and by Maciąg et al. [14] who showed that independent from other risk factors (younger age, low LVEF), wide QRS complexes at the time of ICD implantation may be associated with more frequent appropriate ICD interventions and increased mortality risk. In the present study, we did not find any effect of amiodarone and beta-blocker use, and the indication for ICD on the occurrence of ventricular tachyarrhythmia. Discordant results were reported by Singh et al. [15] who found that only the type of the disease (dilated cardiomyopathy, CAD) was associated with a significant risk of future malignant ventricular arrhythmia in multivariate analysis. Other such markers include advanced patient age, renal dysfunction, obstructive lung disease, diabetes, anxiety, depression, cigarette smoking, no beta-blocker use, no amiodarone use, LVEF < 20%, NYHA class III–IV, and prolonged QT interval [16–19]. Differences between the results of the above studies may be explained by varying patient characteristics and follow-up duration. A novel finding of our study is the importance of mean resting HR > 79 bpm as a predictor of ventricular tachyarrhythmia in patients after ICD implantation.

Inhibitors of the renin–angiotensin–aldosterone system play a major role in the treatment of cardiovascular disease. ACEI and ARB may reduce the risk of ventricular tachyarrhythmia by improving cardiac haemodynamics, inhibiting cardiac remodelling and reducing potassium excretion [20]. Other studies did not confirm benefits of these drugs in terms of reducing the rate of malignant ventricular arrhythmia [21] which is consistent with our findings.

A potential antiarrhythmic effect of statins in both ischemic and non-ischaemic myocardial damage has been noted [22, 23]. Benefits from statins are attributed to their anti-ischaemic, anti-remodelling and anti-inflammatory effects, as well as improvement of endothelial function and stabilisation of sympathetic activity [24]. In our study, we did not find any differences related to the use of this therapy, which might have been related to the fact that statins were taken by a large proportion of patients in our study population.

In nearly 20% of patients, QRS width was ≥ 120 ms, and this group included potential candidates for cardiac resynchronisation therapy (CRT) but implantation of a LV lead was impossible due to technical and/or anatomic problems.

Attempts to implant a CRT device fail in 5–15% of patients in cardiac electrotherapy centres, due to the same reasons as in our patients [25].

Literature data indicate an increased mortality risk, worsening of HF, and frequent hospitalisations among patients with ventricular tachyarrhythmia leading to ICD intervention [26]. In our study, we did not find any effect of ICD interventions on total mortality. This might have been related to both short duration of follow-up and a relatively small annual rate of ICD interventions.

In contrast, we noted an increased rate of ICD interventions among those patients who died due to HF. It may be thus debated whether ICD interventions are the cause of HF progression or ventricular tachyarrhythmia leading to ICD intervention occur more frequently in patients with severe HF (NYHA class III–IV).

The overall rate of appropriate ICD interventions in our study (18%) is similar to that reported in other prospective studies (MADIT II, SCD-HEFT) [2–4]. The same was found regarding the rate of appropriate ICD interventions in primary prevention (20%), while the rate of appropriate interventions in secondary prevention was only 17% as compared to previously reported 50–55% [4]. This might have resulted from the characteristics of our secondary prevention population (only patients with established ischaemic heart disease and/ or dilated cardiomyopathy).

As noted, inappropriate ICD interventions occurred due to rapid ventricular rate in atrial tachyarrhythmias, AF, mostly in patients with a single-chamber ICD. The rate of such interventions in our study (8.2%) was smaller compared to that previously reported in the MADIT and SCD-HEFT studies (12 and 17%, respectively).

From a practical perspective, our findings indicate some benefit from ICD implantation in patients with increased resting HR, NYHA class II or higher HF, and wide QRS. According to guidelines, this patient population would benefit most from implantation of a CRT-D device. Unfortunately, such an attempt failed in these patients. Patients with low LVEF (< 31%) are at particular risk of SCD due to ventricular tachyarrhythmia and this parameter alone can influence the decision regarding ICD implantation. It is important to develop effective methods of predicting ventricular tachyarrhythmia leading to appropriate ICD intervention. Implementation of such methods into ICD devices might allow warning patients of a possible ICD intervention, or even avoiding it by cessation of a particular activity or administering a medication.

Limitations of the study

Limitations of the present study include its retrospective nature, small study sample, and short duration of follow-up. Reliability of our results depends on the accurate data collection at each visit during the follow-up period. In addition, LVEF was not evaluated dynamically, and some data could only be obtained at the time of ICD implantation. It should also be noted that the types and exact sequences of ICD interventions depend largely on ICD programming, and arrhythmia detection algorithms could not be completely standardised due to different therapeutic approaches used by different ICD manufacturers.

CONCLUSIONS

Significant predictors of ventricular tachyarrhythmia/appropriate ICD intervention included reduced LVEF, increased resting HR, NYHA class II or higher HF, and wide QRS. Patients with low LVEF (< 31%) are at particular risk of SCD due to ventricular arrhythmia and this parameter alone can influence the decision regarding ICD implantation. No effect of ICD interventions on total mortality was observed, although more ICD interventions were observed in patients who died due to HF.

Conflict of interest: *none declared*

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Czynniki predysponujące do wystąpienia tachyarytmii komorowej wyzwalającej właściwą interwencję kardiowertera-defibrylatora u osób z chorobą niedokrwienną serca lub nieniedokrwienną kardiomiopatią rozstrzeniową

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Streszczenie

Wstęp: W celu osiągnięcia maksymalnych korzyści z leczenia groźnych arytmii komorowych za pomocą wszczepialnego urządzenia (ICD) bardzo ważne jest zidentyfikowanie parametrów, które predysponują do wystąpienia tachyarytmii komorowej, czyli chorych, u których korzyść z ICD będzie największa. W erze profilaktycznej terapii nagłego zgonu sercowego (SCD) za pomocą ICD i ograniczonych źródeł finansowania opieki zdrowotnej wykrycie dodatkowych markerów predysponujących do pojawienia się arytmii jest potrzebne w celu lepszej selekcji chorych.

Cel: Celem pracy było wykrycie czynników predysponujących do wystąpienia tachyarytmii komorowej wywołującej adekwatną interwencję u osób po wszczepieniu ICD.

Metody: Analizowano 376 chorych (56 kobiet, 320 mężczyzn), w wieku średnio 66,1 ± 11,2 roku (22–89 lat) z wszczepionym w okresie od stycznia 2008 do grudnia 2010 r. ICD bez funkcji resynchronizacji. W tej grupie w ramach profilaktyki pierwotnej ICD implantowano u 275 chorych, a — wtórnej u 101 osób. Retrospektywnie przeanalizowano protokoły operacyjne, dokumentację kliniczną i ambulatoryjną. Analizie poddano spoczynkowe EKG przy przesuwie 25 mm/s i cesze 10 mm/ /1 mV, z których wyliczano średnią szerokość zespołów QRS, spoczynkową częstość rytmu serca (HR) i wewnątrzsercowe EKG zarejestrowane w pamięci ICD, w których oceniano prawidłowość interwencji antyarytmicznych. Analizowano liczbę tachyarytmii komorowych i interwencji ICD. Oceniano następujące parametry kliniczne i techniczne: płeć, wiek, frakcję wyrzutową lewej komory (LVEF), rodzaj profilaktyki SCD (pierwotna, wtórna), typ ICD (jednojamowy — VR, dwujamowy — DR), wykonanie marginesu bezpieczeństwa progu defibrylacji przy wszczepieniu ICD, lokalizację elektrody komorowej (w okolicy drogi odpływu prawej komory, koniuszka prawej komory), średnią HR, szerokość zespołów QRS, klasę NYHA, wystąpienie po wszczepieniu tachyarytmii komorowej powodującej adekwatną interwencję, interwencje ICD, choroby i zaburzenia HR z wywiadów (przebyty zawał serca, kardiomiopatię rozstrzeniową niedokrwienną i nieniedokrwienną, nadciśnienie tętnicze, przebyte migotanie komór, częstoskurcz komorowy utrwalony i nieutrwalony, utrwalone migotanie przedsionków, stan po PCI i/lub CABG) oraz stosowane leki (amiodaron, sotalol, beta-adrenolityki, inhibitory konwertazy angiotensyny/ /antagoniści receptora angiotensyny — ACEI/ARB, statyny, diuretyki pętlowe, inhibitory aldosteronu).

Wyniki: W średnim okresie obserwacji 387 ± 300 (5–1400) dni z 376 badanych z ICD wyodrębniono grupę 68 chorych (61 mężczyzn, 7 kobiet) w wieku średnio 64,7 ± 12,3 roku (22–89), u których wystąpiła tachyarytmia komorowa powodująca adekwatną interwencję ICD. Średni czas do wystąpienia tachyarytmii komorowej wynosił 281 ± 229 (5–972) dni (p < 0,001). W celu uzyskania optymalnej czułości i swoistości cechy diagnostycznej w analizie tachyarytmii komorowej wywołującej adekwatną interwencję *vs.* bez tachyarytmii komorowej i bez adekwatnej interwencji wyznaczono punkty odcięcia, stosując krzywe ROC (*cutoff* dla LVEF = 31%, HR = 79/min). Następnie porównano grupę z tachyarytmią komorową powodującą adekwatną interwencję z pozostałą badaną populacją, uwzględniając wartości punktów odcięcia. Zanotowano istotne różnice w stosunku do LVEF (p < 0,001), HR (p < 0,022), stosowania ACEI/ARB (p < 0,034) i klasy NYHA (p < 0,001). W analizie jednowymiarowej przeprowadzonej metodą Kaplana-Meiera stwierdzono, że istotnymi parametrami zwiększającymi prawdopodobieństwo przeżycia bez tachyarytmii komorowej i bez adekwatnej interwencji są LVEF > 31% (test long--rank p < 0,001), HR ≤ 79/min (test long-rank p < 0,022), szerokość QRS ≤ 114 ms (test long-rank p < 0,045) i II klasa wg NYHA (test long rank p < 0,001). W analizie wielowymiarowej za pomocą modelu regresji Coxa wykazano, że niezależnym parametrem zwiększającym prawdopodobieństwo wystąpienia tachyarytmii komorowej wywołującej adekwatną interwencję jest tylko obniżona LVEF (≤ 31%). Wartość LVEF < 31% istotnie (20-krotnie, p < 0,02) zwiększa prawdopodobieństwo wystąpienia tachyarytmii komorowej do 3 lat po zabiegu wszczepienia ICD. U 68 chorych z tachyarytmią komorową powodującą adekwatną interwencję wystąpiło średnio 4,1 interwencji na osobę w czasie całej obserwacji. W całej populacji liczba interwencji na rok u danej osoby wynosiła 0,28. W całej populacji zanotowano 92 nieadekwatnych interwencji kardiowersji. Wszystkie były skutkiem szybkiej akcji komór w przebiegu migotania przedsionków. Nie stwierdzono wpływu interwencji na śmiertelność całkowitą. Większą częstość występowania interwencji adekwatnych zanotowano u osób zmarłych z powodu niewydolności serca.

Wnioski: Do istotnych predyktorów zwiększających prawdopodobieństwo wystąpienia tachyarytmii komorowej wywołującej adekwatną interwencję ICD należą: obniżona LVEF, zwiększona średnia spoczynkowa HR, > II klasa wg NYHA oraz poszerzony zespół QRS. Chorzy z niską LVEF (< 31%) są szczególnie narażeni na wystąpienie SCD w przebiegu tachyarytmii komorowej i jako odosobniony ten parametr może wpływać na decyzję o implantacji ICD. Nie stwierdzono wpływu interwencji ICD na śmiertelność całkowitą, natomiast wykazano zwiększoną częstość ich występowania u osób zmarłych z powodu niewydolności serca.

Słowa kluczowe: kardiowerter-defibrylator, predyktory wystąpienia tachyarytmii komorowej, interwencje ICD

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