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Determinants of patient survival rate after implantation of a cardioverter-defibrillator without resynchronisation capability

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Abstract

Background: Proper selection of patients at high risk for sudden cardiac death (SCD) and increasing use of implantable cardioverter-defibrillators (ICD) may contribute to improved survival among patients at the highest SCD risk.

Aim: To assess patient survival rate after implantation of an ICD without resynchronisation capability in our own patient population. Using uni- and multivariate analysis, we attempted to identify factors associated with significant worsening of patient survival rate.

Methods: From the population of patients who underwent ICD implantation for primary or secondary prevention of SCD in 2008–2010, we selected 376 patients with coronary artery disease or dilated cardiomyopathy (56 females, 320 males). Mean age was 66.1 ± 11.2 (range 22–89) years. ICD implantation protocols and in-hospital and outpatient records were reviewed retrospectively. We analysed the following clinical and procedural variables: age, gender, left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) functional class, mean heart rate (HR), QRS width, number of antiarrhythmic ICD interventions, type of SCD prevention, ICD type, performing defibrillation threshold testing (DFT) to establish defibrillation safety margin at ICD implantation, ventricular lead location, history of cardiovascular disease and arrhythmia, medications used (amiodarone, sotalol, beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, statins, loop diuretics, aldosterone antagonists). Date and cause of death were established by contacting patient family and/or the hospital to which the patient was admitted shortly before death or the general practitioner caring for the patient (verification of death certificates).

Results: During the mean follow-up period of 447 ± 313 days, 46 patients died of known causes. Causes of death included sudden death in 16 patients, heart failure in 20 patients, and other causes in 10 patients (respiratory failure — 1, bleeding diathesis — 2, lung cancer — 3, colorectal cancer — 1, traffic accident — 1, and stroke — 2 patients). A comparison between primary and secondary prevention patients was performed. Mean QRS width < 118 ms, resting HR < 78 bpm and LVEF > 30% were significant cutoff values for improved survival as determined using the ROC curves. HR > 78 bpm was observed in all SCD patients. In Kaplan-Meier univariate analysis including 27 parameters potentially influencing survival, 10 significant parameters were identified (type of prevention, presence of cardiomyopathy, ventricular tachycardia, HR, QRS width, LVEF, NYHA class, performing DFT, and statin and diuretic treatment). In Cox multivariate analysis, risk of death was increased with mean LVEV < 30% (3-fold increase in risk), no DFT (2-fold increase in risk), NYHA class III or IV (3-fold increase in risk), and no statin use (2-fold increase in risk). Mean HR < 78 bpm and QRS width < 118 ms were independently related to an increased survival.

Conclusions: Death rate was higher in patients with LVEF < 30%, NYHA class III or IV, no DFT performed and no statin treatment. In these patients, indications for cardiac resynchronisation therapy should be considered. HR < 78 bpm and QRS width < 118 ms are independent protective factors. HR > 78 bpm was observed in all SCD patients. Sicker ICD patients live for a shorter time. The presence of atrial fibrillation, number of antiarrhythmic ICD interventions, ICD type and revascularisation approach did not affect survival/mortality.

Key words: mortality, implantable cardioverter-defibrillator (ICD), parameters affecting survival

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INTRODUCTION

According to the current guidelines on the secondary prevention of sudden cardiac death (SCD), implantable cardioverter-defibrillator (ICD) should be used in patients following a ventricular fibrillation (VF) or haemodynamically unstable ventricular tachycardia (VT) event (class I recommendation, level of evidence A). In the primary prevention of SCD, ICD should be implanted in patients with ischaemic dilated cardiomyopathy (IDCM) with left ventricular ejection fraction (LVEF) ≤ 35% at least 40 days after myocardial infarction (MI) (class I recommendation, level of evidence A), and in patients with nonischaemic dilated cardiomyopathy (NIDCM) with LVEF ≤ 35% (class I recommendation, level of evidence B). In each of these categories, patients should receive optimal drug therapy and be expected to survive more than a year with overall good functional status [1–8]. ICD treatment results in a significant reduction of mortality and hospitalisation rate. VT events are usually terminated impercetibly for the patient with antitachycardia pacing (ATP), while ATP-resistant VT and VF are cardioverted with a single ICD shock. Prospective, randomised clinical trials clearly showed that ICD treatment is superior to antiarrhythmic drug therapy in patients who have survived a cardiac arrest, and result in an additional reduction in mortality in patients with IDCM or NIDCM compared to benefits provided by optimal antiarrhythmic treatment. With ICD treatment, total mortality in primary and secondary prevention is reduced by about 20%, and arrhythmic mortality in patients after MI is reduced by about 50% [7–10].

ICD implantation should be considered, however, in the context of a comprehensive and often difficult diagnostic and therapeutic approach. ICD provides only symptomatic treatment and does not reduce the risk of adverse arrhythmic events. Better selection of patients at high risk for SCD and increasing availability of ICD treatment may contribute to improved survival among patients at the highest SCD risk. However, we are still unable to identify such patients in an optimal way.

The aim of this study was to assess patient survival rate after ICD implantation without resynchronisation function in our own patient population. We identified factors related to significant worsening of patient survival rate in uni- and multivariate analyses.

METHODS

The study population included 376 patients (56 females, 320 males) aged 66.1 ± 11.2 (range 22–89) years who underwent implantation of an ICD without resynchronisation capability for primary or secondary prevention of SCD in 2008–2010. The inclusion criteria were as follows:

- coronary artery disease or NIDCM with an ICD implanted for primary or secondary prevention of SCD;
- complete in-hospital and outpatient records (at least three follow-up visits at an ICD clinic, with printed device interrogation reports and resting electrocardiograms [ECGs]);
- regular patient contact with the ICD clinic;
- established cause of death in those patients who died.

Coronary artery disease was diagnosed based on echocardiography and/or coronary angiography or a history of MI, and NIDCM was diagnosed based on echocardiography and/or coronary angiography. Secondary prevention group included patients with a history of VF or haemodynamically unstable sustained VT due to coronary artery disease or NIDCM. Patient characteristics are shown in Tables 1A and 1B.

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 possible required changes in device programs, 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, lead resistance, and appropriateness of ICD interventions were assessed during each follow-up visit. We analysed resting ECGs at 25 mm/s and 10 mm/1 mV to calculate average QRS width and resting heart rate (HR), and intracardiac electrograms stored in the ICD memory to evaluate appropriateness of ICD interventions (ATP, cardioversion). In case of chronic atrial fibrillation (AF), a mean of 2 shortest and longest RR intervals was calculated, and mean HR was calculated or read from the ECG machine. 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.

Table 1A. Characteristics of the study group

Parameter	N	Per cent	Mean	SD	Median	Min.	Max.
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
No. of inappropriate interventions	31	8.2	3	2.3	2	1	11
No. of appropriate interventions	68	18.1	4.1	9.7	2	1	60

Table 1B. Characteristics of the study group (continued)

Parameter	N (%)
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 MI	206 (54.8%)
Dilated cardiomyopathy (DCM, ICM)	333 (88.6%)
Arterial hypertension	119 (31.6%)
Ventricular fibrillation	61 (16.2%)
Sustained or nsVT	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 antagonist; CABG — coronary artery bypass grafting; DCM — dilated cardiomiopathy; DFT — defibrillation threshold testing; ICM — ischaemic cardiomiopathy; ICD — implantable cardioverter-defibrillator; MI — myocardial infarction; NYHA — New York Heart Association; PCI — percutaneous coronary intervention; RV — right ventricle; RVOT — right ventricular outflow tract; nsVT — non-sustained ventricular tachycardia

We analysed the following clinical and technical variables: gender, age, LVEF, mean HR, QRS width, New York Heart Association (NYHA) functional class, number of appropriate and inappropriate antiarrhythmic ICD interventions, type of SCD prevention, ICD type, performing defibrillation threshold testing (DFT) to establish defibrillation safety margin at ICD implantation, ventricular lead location, history of cardiovascular disease and arrhythmia (previous MI, IDCM, NIDCM, arterial hypertension, previous VF, sustained or non-sustained VT, chronic AF, previous percutaneous coronary intervention and/or coronary artery bypass grafting [CABG]), and medications used (amiodarone, sotalol, beta-blockers, angiotensin-converting enzyme [ACE] inhibitors/angiotensin receptor blockers, statins, loop diuretics, aldosterone antagonists).

Location of the ICD lead within the right ventricular outflow tract septum was verified using ECG (negative paced QRS complexes in lead I and positive QRS complexes in lead aVF) and fluoroscopic left anterior oblique (LAO) 40 degree view during ICD implantation [11].

Date and cause of death were established by contacting patient family and/or the hospital to which the patient was admitted shortly before death or the general practitioner caring for the patient (verification of death certificates).

The protocol of this follow-up study, including contacting patients and/or their families to obtain information regarding their health status for research purposes, 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, N_1, N_2). 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 cross. 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. Kaplan-Meier survival curves were used to evaluate survival time from ICD implantation to death or the last follow-up visit depending on the value of a specific dichotomous variable. Significance of the differences between survival curves for the two 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 survival were identified and included stepwise into a multivariate Cox proportional hazard model. 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 Microsoft Office Excel.

RESULTS

Among 376 patients included into the study, 46 patients died (Table 2) during the mean follow-up period of 447 ± ± 313 days (median 401 days, range 15–1400 days). Causes of death included: sudden death in 16 patients (at mean 273 ± 258 days), heart failure (HF) in 20 patients (at 480 ±

Table 2. Patient number (n), age, and living status (survivors vs. non-survivors) in primary and secondary prevention groups

Living status	Primary prevention Patient number and age			Secondary prevention Patient number and age			Overall			P
	N	Mean ± SD	Min–max	N	Mean ± SD	Min–max	N	Mean ± SD	Min–max	
Survivors	239	65.9 ± 11.3	25–89	91	65.3 ± 11.4	22–87	330	65.7 ± 11.3	22–89	0.654
Non-survivors	36	67.7 ± 10.3	43–86	10	72.7 ± 9.8	51–84	46	68.8 ± 10.3	43–86	0.178
Overall	275	66.1 ± 11.2	25–89	101	66.0 ± 11.4	22–87	376	66.1 ± 11.2	22–89	0.922
P		0.362			0.050			0.081		–

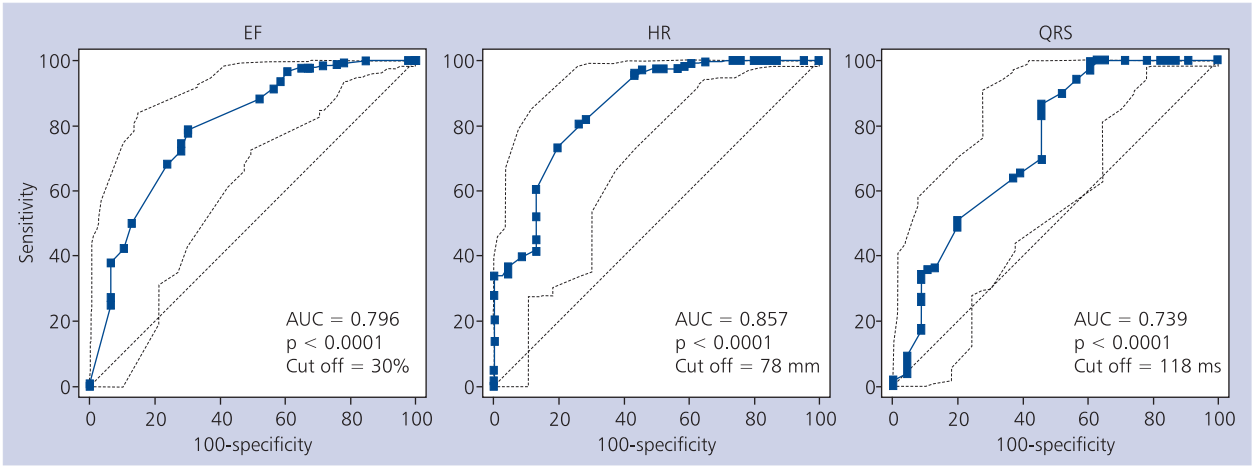

Figure 1. Receiver operating characteristic curves with cutoff points for left ventricular ejection fraction (EF), heart rate (HR), and QRS width for predicting survival/mortality. Areas under curve (AUC) are given along with their statistical significance (p) and the cutoff value

± 294 days), and other causes in 10 patients (at 494 ± 396 days), including respiratory failure in 1 patient, bleeding diathesis in 2 patients, lung cancer in 3 patients, colorectal cancer in 1 patient, traffic accident in 1 patient, and stroke in 2 patients (insignificant difference between mean times to death, $p < 0.09$). Mean QRS width < 118 ms, resting HR < 78 bpm and LVEF > 30% were significant cutoff values for improved survival as determined using the ROC curves (Fig. 1). Table 3A–C shows differences in the evaluated parameters, history of cardiovascular disease and arrhythmia, and medications used between patients who died and those who survived. Table 4 shows comparison between primary and secondary prevention in regard to mortality and associated factors. Primary prevention patients were characterised by increased HR, increased QRS width, and more frequent cardioversions by a single ICD shock, non-sustained VT, chronic AF, IDCM, and a history of CABG. Those patients were more frequently treated with loop diuretics and aldosterone antagonists as compared to the primary prevention group. Estimated Kaplan-Meier survival curves were plotted to determine survival probability among ICD patients in the subsequent years of follow-up. Univariate analyses yielded 10 significant parameters among 27 evaluated potential factors affecting survival (Fig. 2A–C). Next, 6 of these parameters were identified as significant in a multivariate analysis when included stepwise into the Cox model. Results are shown in Table 5. Risk of death was increased with mean LVEF < 30% (3-fold increase in risk), no DFT (2-fold increase in risk), NYHA class III or IV (3-fold increase in risk), and no statin use (2-fold increase in risk). Mean HR < 78 bpm and QRS width < 118 ms were independently related to a decreased risk of death.

In regard to defibrillation safety margin as established by DFT, VF was effectively terminated by a single 15 J shock in 125 patients, and by two 20 J shocks in 52 patients. In 5 patients, minimal energy was above 20 J. DFT showed a 10 J safety margin in all tested patients. We did not analyse patient survival in regard to differences in DFT results.

The most frequent causes of not performing DFT at ICD implantation were low blood pressure (in 23% of patients), AF and inability to exclude a left atrial thrombus (in 27%), left ventricular thrombus (in 4%), severe congestive HF (in 6%),

Table 3A. Differences in evaluated parameters between non-survivors and survivors

Parameter		Non-survivors		Survivors		Overall		P
		N_1	%	N_2	%	n	%	
Gender	Female	9	19.6	47	14.2	56	14.9	0.342
	Male	37	80.4	283	85.8	320	85.1	
Age* [years]	≤ 63	14	30.4	148	44.8	162	43.1	0.064
	> 63	32	69.6	182	55.2	214	56.9	
Ejection fraction* [%]	≤ 30	32	69.6	70	21.2	102	27.1	**< 0.001**
	> 30	14	30.4	260	78.8	274	72.9	
Heart rate* [bpm]	≤ 78	12	26.1	266	80.6	278	73.9	**< 0.001**
	> 78	34	73.9	64	19.4	98	26.1	
NYHA class	II	2	4.3	83	25.1	85	22.6	
	III	20	43.4	208	63.0	228	60.6	**< 0.001**
	IV	24	52.3	39	11.9	63	16.7	
QRS width* [ms]	≤ 118	21	45.7	286	86.7	307	81.6	**< 0.001**
	> 118	25	54.3	44	13.3	69	18.4	
Intervention (ATP, CV)	Yes	10	21.7	58	17.6	68	18.1	0.491
	No	36	78.3	272	82.4	308	81.9	
Prevention type	Primary	36	78.3	239	72.4	275	73.1	0.403
	Secondary	10	21.7	91	27.6	101	26.9	
ICD type	DR	22	47.8	139	42.1	161	42.8	0.464
	VR	24	52.2	191	57.9	215	57.2	
DFT	Yes	18	39.1	164	49.7	182	48.4	0.179
	No	28	60.9	166	50.3	194	51.6	
Lead location	RVOT	29	63.0	224	67.9	253	67.3	0.513
	RV apex	17	37.0	106	32.1	123	32.7	
No. of ATP interventions	1	3	37.5	20	50.0	23	47.9	
	> 1	5	62.5	20	50.0	25	52.1	0.703
	Total	8	100.0	40	100.0	48	100.0	
No. of CV interventions	1	2	40.0	18	64.3	20	60.6	
	> 1	3	60.0	10	35.7	13	39.4	0.360
	Total	5	100.0	28	100.0	33	100.0	

*Cutoff values for death/survival identified using receiver operating characteristics (ROC) curves; ATP — antitachycardia pacing; CV — cardioversion; DFT — defibrillation threshold testing; ICD — implantable cardioverter-defibrillator; NYHA — New York Heart Association; RV — right ventricle; RVOT — right ventricular outflow tract

acute ischaemia (in 3%), lack of anaesthesiology support (in 23%), and unknown causes (in 14% of patients).

We also analysed factors predisposing to SCD in a subpopulation of 16 patients who died suddenly (Table 6). All these patients were characterised by a resting HR > 78 bpm and less statin use compared to other patients. Results in the subpopulation of 20 patients who died due to HF were similar to the overall study group.

An attempt to implant a cardiac resynchronisation therapy (CRT) lead failed in 49 (13%) patients in our study population.

DISCUSSION

Heart failure is the major cause of death in patients with implanted ICD, as was also the case among patients in our study. Despite optimal drug therapy and invasive treatment, HF gradually progressed with longer disease duration, ultimately leading to death. Mean yearly all-cause mortality in the study population was about 12%, consistent with mortality rates in a population of 2134 patients reported by Welsenes et al. [12]. QRS width > 118 ms was noted in nearly 20% of patients. The latter subgroup included potential candidates for CRT. Unfortunately, a left ventricular lead could not be

Table 3B. Differences in the rates of cardiovascular disease and arrhythmia between non-survivors and survivors

Cardiovascular disease and arrhythmia		Non-survivors		Survivors		Overall		P
		N_1	%	N_2	%	n	%	
Previous MI	Yes	24	52.2	182	55.2	206	54.8	0.704
	No	22	47.8	148	44.8	170	45.2	
Dilated cardiomyopathy (DCM and ICM)	Yes	44	95.7	289	87.6	333	88.6	0.107
	No	2	4.3	41	12.4	43	11.4	
Arterial hypertension	Yes	14	30.4	105	31.8	119	31.6	0.850
	No	32	69.6	225	68.2	257	68.4	
Ventricular fibrillation	Yes	5	10.9	56	17.0	61	16.2	0.293
	No	41	89.1	274	83.0	315	83.8	
Sustained and non-sustained ventricular tachycardia	Yes	33	71.7	184	55.8	217	57.7	**0.040**
	No	13	28.3	146	44.2	159	42.3	
Chronic atrial fibrillation	Yes	8	17.4	94	28.5	102	27.1	0.113
	No	38	82.6	236	71.5	274	72.9	
Previous PCI	Yes	7	15.2	82	24.8	89	23.7	0.150
	No	39	84.8	248	75.2	287	76.3	
Previous CABG	Yes	3	6.5	39	11.8	42	11.2	0.285
	No	43	93.5	291	88.2	334	88.8	
Overall		46	100.0	330	100.0	376	100.0	

CABG — coronary artery bypass grafting; DCM — dilated cardiomiopathy; ICM — ischaemic cardiomiopathy; MI — myocardial infarction; PCI — percutaneous coronary intervention

Table 3C. Differences in drug therapy between non-survivors and survivors

Drug		Non-survivors		Survivors		Overall		P
		N_1	%	N_2	%	n	%	
Amiodarone	Yes	9	19.6	64	19.4	73	19.4	0.978
	No	37	80.4	266	80.6	303	80.6	
Sotalol	Yes	0	0.0	14	4.2	14	3.7	0.154
	No	46	100.0	316	95.8	362	96.3	
Beta-blocker	Yes	41	89.1	290	87.9	331	88.0	0.806
	No	5	10.9	40	12.1	45	12.0	
ACEI/ARB	Yes	35	76.1	248	75.2	283	75.3	0.890
	No	11	23.9	82	24.8	93	24.7	
Statin	Yes	25	54.3	239	72.4	264	70.2	**0.012**
	No	21	45.7	91	27.6	112	29.8	
Loop diuretic	Yes	38	82.6	198	60.0	236	62.8	**0.003**
	No	8	17.4	132	40.0	140	37.2	
Aldosterone antagonist	Yes	37	80.4	220	66.7	257	68.4	0.060
	No	9	19.6	110	33.3	119	31.6	
Overall		46	100.0	330	100.0	376	100.0	

ACEI — angiotensin-converting enzyme inhibitor; ARB — angiotensin receptor antagonist

Table 4. Comparison of primary and secondary prevention

Parameter		Primary prevention		Secondary prevention		Overall		P
		N_1	%	N_2	%	n	%	
Total number of deaths		36	13.1	10	9.9	46	12.2	0.403
Ejection fraction*	≤ 30%	77	28.0	28	27.7	105	27.9	0.958
	> 30%	198	72.0	73	72.3	271	72.1	
Herat rate*	≤ 78 bpm	201	73.1	83	82.2	284	75.5	0.069
	> 78 bpm	74	26.9	18	17.8	92	24.5	
QRS width*	≤ 118 ms	173	62.9	78	77.2	251	66.8	**0.009**
	> 118 ms	102	37.1	23	22.8	125	33.2	
NYHA class	II	59	21.4	26	25.8	85	22.6	
	III	169	61.5	59	58.4	228	60.6	0.676
	IV	47	17.1	16	15.8	63	16.8	
Ischaemic cardiomyopathy		179	65.1	58	57.4	237	63.0	0.172
Non-ischaemic cardiomyopathy		79	28.7	13	12.9	92	24.5	**0.001**
Previous myocardial infarction		150	54.5	56	55.4	206	54.8	0.876
Sustained and non-sustained VT		178	64.7	39	38.6	217	57.7	**< 0.001**
Ventricular fibrillation		0	0.0	61	60.4	61	16.2	**< 0.001**
Chronic atrial fibrillation		82	29.8	20	19.8	102	27.1	**0.053**
No beta-blocker use		29	10.5	16	15.8	45	12.0	0.161
No amiodaron use		232	84.4	71	70.3	303	80.6	**0.002**
No statin use		82	29.8	30	29.7	112	29.8	0.983
No loop diuretic use		93	33.8	47	46.5	140	37.2	**0.024**
No aldosterone antagonist use		78	28.4	41	40.6	119	31.6	**0.024**
No ACEI/ARB use		66	24.0	27	26.7	93	24.7	0.586
Previous CABG		36	13.1	6	5.9	42	11.2	**0.051**
Previous PCI		67	24.4	22	21.8	89	23.7	0.602
Any ICD intervention		48	17.5	20	19.8	68	18.1	0.600
ICD intervention — cardioversion		23	8.3	10	9.9	33	8.7	**0.026**
Overall		275	100.0	101	100.0	376	100.0	

*Cutoff values for death/survival identified using receiver operating characteristics (ROC) curves; ACEI — angiotensin-converting enzyme inhibitor; ARB — angiotensin receptor antagonist; CABG — coronary artery bypass grafting; NYHA — New York Heart Association; PCI — percutaneous coronary intervention; VT — ventricular tachycardia

effectively implanted due to lack of access to coronary sinus, high pacing threshold of the left ventricular lead, phrenic nerve stimulation and intraoperative dislocation of the left ventricular lead, or lack of an adequately sized vein. Literature data indicate that CRT lead cannot be effectively implanted in 5–15% of patients, due to the same technical problems as in our study [13].

Cardiovascular mortality is reduced by decreasing the number of sudden deaths, but such deaths are not eliminated completely. In the MADIT II study, 3.6% of patients died suddenly [7, 14]. Causes of sudden deaths in patients with an implanted ICD include ineffective defibrillation due to an increase in defibrillation threshold above maximal ICD shock energy, battery depletion, ICD failure or shutdown, lead damage, failure to recognise arrhythmia, electromechanical dissociation, pacing failure, and other causes of sudden deaths (e.g., MI, pulmonary embolism) [7, 14–16]. In our study population, the mean time to sudden death was insignificantly shorter than the mean time to death due to HF. In all patients in our study who died suddenly, mean resting HR was > 78 bpm, and statin use was reduced. Unfortunately, we were unable to obtain intracardiac electrograms recorded by ICD and thus it is unknown whether these deaths were due to arrhythmic events and if so, whether they resulted from lack of device activation or a failure of ICD to terminate the arrhythmia.

The final regression model included 6 significant predictors of mortality risk (decreased survival), including no DFT,

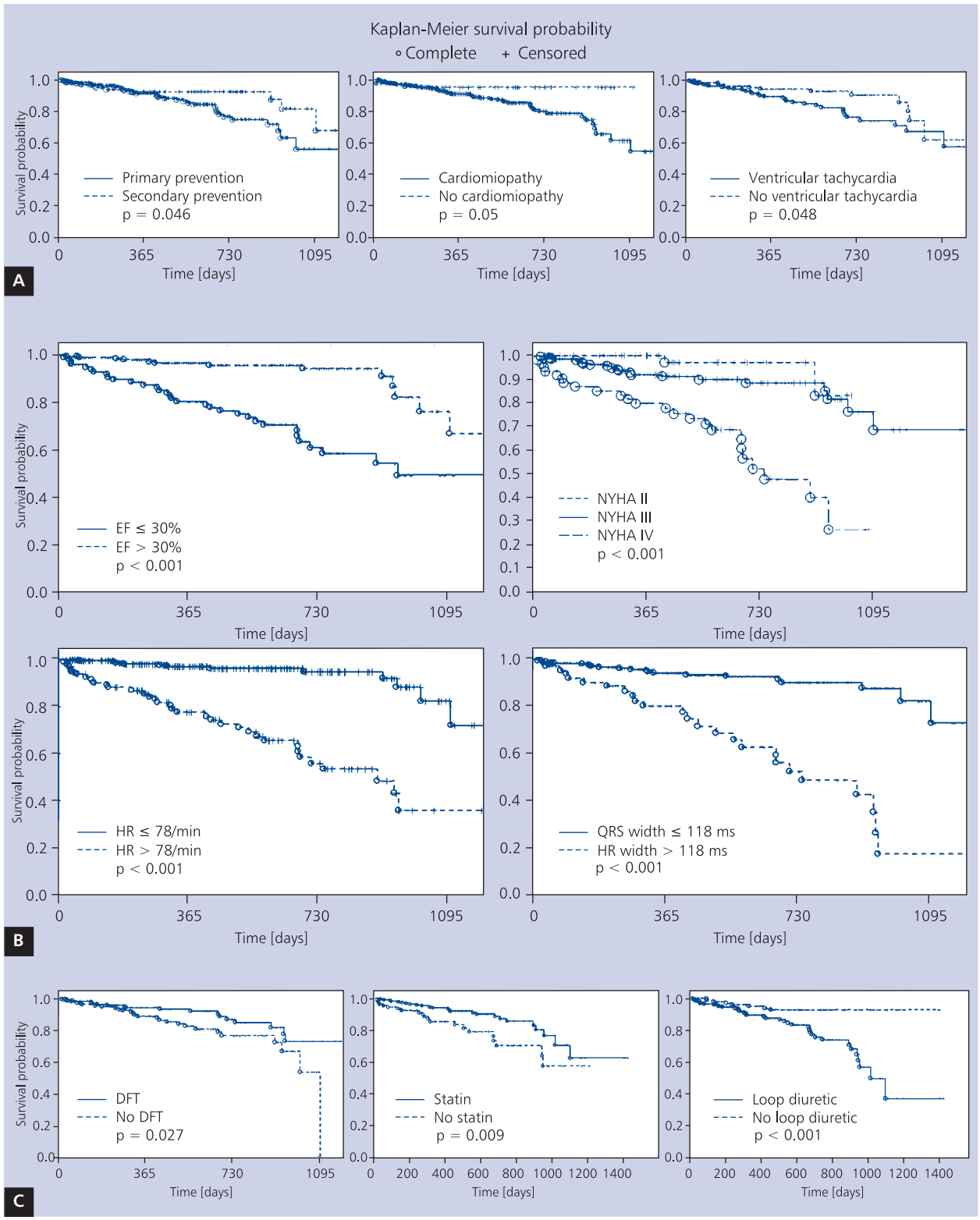

Figure 2. **A.** Kaplan-Meier survival curves in patient groups depending on the prevention type, the presence of cardiomyopathy, and the occurrence of ventricular tachycardia. Log rank test; **B.** Kaplan-Meier survival curves in patient groups depending on heart rate (HR), QRS width, left ventricular ejection fraction (EF), and New York Heart Association (NYHA) functional class. Log rank test; **C.** Kaplan-Meier survival curves in patient groups depending on performing defibrillation threshold testing (DFT), statin use, and diuretic use. Log rank test

Table 5. Parameters significantly related to survival in Cox multivariate logistic regression analysis

Parameter	Regression coefficient	P	Hazard ratio	Lower limit of 95% CI	Upper limit of 95% CI
EF ≤ 30%	0.5508	0.0017	3.0092	1.5141	5.9806
HR ≤ 78 bpm	–0.7216	0.0002	0.2362	0.1094	0.5099
QRS width ≤ 118 ms	–0.4696	0.0043	0.3910	0.2051	0.7452
NYHA class III–IV	1.141	0.003	3.130	1.481	6.613
No DFT	0.3885	0.0145	2.1748	1.1665	4.0545
No statin use	0.3745	0.0146	2.1150	1.1592	3.8591

CI — confidence interval; DFT — defibrillation threshold testing; EF — ejection fraction; HR — heart rate; NYHA — New York Heart Association

Table 6. Comparison of characteristics of patients who died suddenly and those who died due to heart failure and other known causes

Parameter	Heart failure and other causes of death		Sudden death		Overall		P
	N_1	%	N_2	%	n	%	
EF* ≤ 30%	19	63.3	13	81.3	32	69.6	0.316
EF* > 30%	11	36.7	3	18.8	14	30.4	
HR* ≤ 78 bpm	13	43.3	0	0.0	13	28.3	**0.002**
HR* > 78 bpm	17	56.7	16	100.0	33	71.7	
QRS width* ≤ 118 ms	10	33.3	11	68.8	21	45.7	**0.031**
QRS width* >118 ms	20	66.7	5	31.3	25	54.3	
NYHA class II	2	6.7	0	0.0	2	4.3	
NYHA class III	11	36.7	9	56.3	20	43.5	0.313
NYHA class IV	17	56.7	7	43.8	24	52.2	
Previous MI	20	66.7	4	25.0	24	52.2	**0.012**
Chronic atrial fibrillation	6	20.0	2	12.5	8	17.4	0.694
Secondary prevention	7	23.3	3	18.8	10	21.7	0.999
All ICD interventions	13	43.3	3	18.8	16	34.8	0.117
Appropriate ICD interventions	7	23.3	3	18.8	10	21.7	0.999
No beta-blocker use	4	13.3	1	6.3	5	10.9	0.644
No amiodarone use	25	83.3	12	75.0	37	80.4	0.698
No statin use	11	36.7	10	62.5	21	45.7	**0.094**
No ACEI/ARB use	6	20.0	5	31.3	11	23.9	0.394
Overall	30	100.0	16	100.0	46	100.0	

*Cutoff values for death/survival identified using receiver operating characteristics (ROC) curves; ACEI — angiotensin-converting enzyme inhibitor; ARB — angiotensin receptor antagonist; EF — ejection fraction; HR — heart rate; ICD — implantable cardioverter-defibrillator; MI — myocardial infarction NYHA — New York Heart Association

no statin use, mean LVEF ≤ 30%, QRS width > 118 ms, resting HR > 78 bpm, and NYHA class III or IV. Only few previous studies investigated outcomes in patients who do not undergo DFT at ICD implantation. It is thus unknown what the long-term outcomes would be if DFT at ICD implantation were eliminated completely. In retrospective analyses, Pires and Johnson [17] and Hall et al. [18] found that all-cause mortality among patients who did not undergo intraoperative testing of defibrillation effectiveness was significantly higher than among those undergoing DFT to determine defibrillation safety margin. Our present findings, as well as previous findings in another group of patients [19] are similar to the above results (increased survival among patients undergoing DFT) and suggest that if possible, defibrillation safety margin should be secured. This may be not an unexpected finding as patients who did not undergo DFT were likely to be more severely ill and thus at a higher risk of VF. Ventricular tachyarrhythmia events that remained untreated

due to programming errors were reported in the literature. It is believed that such events may be a cause of SCD in some patients. Clearly, the ICD lead may dislocate or its distal end may be inappropriately placed, leading to ineffective ICD impulses. For these reasons, assessing defibrillation safety margin at ICD implantation remains a standard procedure [16–20]. A much larger prospective randomised clinical trial would be required to obviate the need for DFT.

Appropriate treatment of underlying cardiac disorder, including drug therapy, is important to improve unfavourable outcomes regarding the occurrence of SCD. The risk of SCD was clearly shown to be reduced by such drugs as beta-blockers, antithrombotic drugs, ACE inhibitors, statins, and spironolactone. In our study, we noted a trend ($p < 0.06$) for a benefit from the use of aldosterone antagonists. In addition to the established effects of these drugs on the water and electrolyte balance, their non-renal effects have been highlighted such as reducing fibrosis, coronary inflammation and oxidative stress, improving vascular endothelial function, and inhibiting platelet aggregation and activation of matrix metalloproteinases. A beneficial effect has also been shown on the HR variability along with reduction of sympathetic activity. These drugs also have a role in reducing the rate of life-threatening ventricular arrhythmia in patients with ICD [9, 21, 22]. Similar relationships were observed for statins.

In the SCD-HeFT trial [8], ICD implantation was shown to reduce mortality risk in patients with reduced LVEF either following a MI or due to non-ischaemic cardiomyopathy. Of note, the LVEF threshold of ≤ 35% was higher than in the MADIT II trial [1, 7]. In our analysis, the cutoff LVEF value associated with reduced survival was ≤ 30%, similarly to the MADIT II findings. In our study population, LVEF values below this threshold were associated with increased mortality, indicating severe left ventricular dysfunction and its likely further progression. Unfortunately, these studies have been retrospective in nature and LVEF was not evaluated dynamically, similarly to other haemodynamic parameters during follow-up.

Borleffs et al. [23] previously defined predictors of increased mortality risk in patients with ischaemic or non-ischaemic cardiomyopathy after ICD implantation for primary prevention. These included AF, LVEF ≤ 25%, NYHA class III or IV, renal dysfunction, advanced age, smoking, diabetes, and QRS width ≥ 130 ms. These risk factors were also identified in the MADIT II and MUSTT studies [1, 2, 7] which were multicentre, prospective, randomised clinical trials performed in populations above 1000 patients.

In our study, we showed worse outcomes associated with QRS width > 118 ms and resting HR > 78 bpm. QRS duration, indicating electrical activation of the ventricles, has been long considered a risk factor for mortality and an indicator of HF severity. With wide QRS complexes, larger repolarisation dispersion is associated with an increased risk of sudden death due to VF, and ventricular asynchrony reduces effectiveness of cardiac work. QRS width > 120 mg is associated with worse outcomes in the Heart Failure Survival Score (HFSS) [24]. Such patients require CRT in addition to ICD (CRT with defibrillator capability).

Large epidemiological studies performed within the last 25 years confirmed the importance of resting HR as an independent predictor of all-cause and cardiovascular mortality in male and female patients both in the general population and among subjects with established cardiovascular disease [25]. Our findings are consistent with these data.

In univariate Kaplan-Meier analysis, adverse prognostic parameters included primary prevention (increased HR, increased QRS width, non-sustained VT, chronic AF, non-ischaemic cardiomyopathy, NYHA class III or IV), VT, and the use loop diuretics. These parameters are strongly associated with progressive HF. The most commonly used loop diuretic in HF is furosemide. When used in large doses, it may lead to reflex activation of the sympathetic nervous system and the renin–angiotensin–aldosterone system, inhibition of the parasympathetic nervous system, and baroreceptor dysfunction. These mechanisms, along with hypokalaemia induced by diuretic treatment, may be responsible for ventricular arrhythmia and ultimately cardiovascular death.

Limitations of the study

Limitations of the present study include its retrospective nature, small study sample, and short duration of follow-up. Exact causes of sudden death could have not been established. It cannot be excluded that some or even all of them were due to arrhythmia, which might have influenced the study results. Low number of deaths limits the ability to identify predictors of mortality using logistic regression analysis. An attempt to implant a CRT lead failed in 13% of patients in our study population, which might have affected mortality analysis.

Of note, however, our study population included patients with complete medical records and under regular outpatient surveillance, which significantly increases the value of our findings.

CONCLUSIONS

In a group of patients with an ICD implanted for primary or secondary prevention of SCD, increased mortality was associated with NYHA class III or IV, decreased LVEF, no DFT testing, and no statin use. Indications for CRT should be considered in a large proportion of these patients.

Decreased HR (within the normal range) and narrow QRS complexes were independent protective factors. Increased resting HR was observed in all primary and secondary prevention ICD patients who suffered a SCD.

We found no significant effect of chronic AF, ICD interventions, ICD type and myocardial revascularisation approach on survival/mortality.

Conflict of interest: *none declared*

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Analiza przeżycia chorych po implantacji kardiowertera-defibrylatora bez resynchronizacji

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Streszczenie

Wstęp: Skuteczna selekcja osób z wysokim ryzykiem nagłego zgonu sercowego (SCD) i większa dostępność zabiegów implantacji kardiowertera-defibrylatora (ICD) daje nadzieję na poprawę przeżywalności pacjentów najbardziej obciążonych kardiologicznie.

Cel: Celem pracy była ocena przeżywalności chorych po implantacji ICD bez funkcji resynchronizacji w materiale własnym kliniki. W analizie jedno- i wieloczynnikowej wyznaczono parametry, które istotnie wpływają na czas przeżycia pacjentów.

Metody: Z populacji chorych z wszczepionym w latach 2008–2010 ICD bez funkcji resynchronizacji w ramach profilaktyki wtórnej lub pierwotnej SCD wyodrębniono 376 osób (56 kobiet, 320 mężczyzn) w średnim wieku 66,1 ± 11,2 roku (22–89 lat) z chorobą niedokrwienną serca lub kardiomiopatią rozstrzeniową nieniedokrwienną. Retrospektywnie przeanalizowano protokoły operacyjne, dokumentację kliniczną i ambulatoryjną. Analizowano parametry kliniczne i techniczne: płeć, wiek, frakcję wyrzutową lewej komory (LVEF), klasę NYHA, średnią częstość rytmu serca (HR), szerokość zespołów QRS, liczbę interwencji antyarytmicznych ICD, rodzaj profilaktyki SCD, typ ICD, oznaczenie marginesu bezpieczeństwa progu defibrylacji (DFT) przy wszczepieniu ICD, lokalizację elektrody komorowej, choroby i zaburzenia HR z wywiadów (zawał, kardiomiopatia, nadciśnienie tętnice, migotanie komór, częstoskurcz komorowy, migotanie przedsionków, stan po PCI i/lub CABG) oraz stosowane leki (amiodaron, sotalol, beta-adrenolityki, ACEI/ARB, statyny, diuretyki pętlowe, inhibitory aldosteronu). Datę i przyczynę zgonu ustalano po skontaktowaniu się z rodziną zmarłego i/lub z oddziałem szpitalnym, na którym przebywał badany tuż przed zgonem, lub lekarzem podstawowej opieki zdrowotnej (weryfikacja kart przyczyn zgonów).

Wyniki: W czasie obserwacji wynoszącej średnio 447 ± 313 dni zmarło 46 chorych ze znanych przyczyn, do których należały: nagły zgon (16 osób), niewydolność serca (20 osób) oraz inne (10 osób, niewydolność oddechowa — 1, skaza krwotoczna — 2, rak płuca — 3, rak jelita grubego — 1, wypadek komunikacyjny — 1, udar mózgu — 2). Porównano profilaktykę pierwotną i wtórną pod względem umieralności i czynników z nią związanych. Średnia szerokość QRS < 118 ms, spoczynkowy HR < 78/min i LVEF > 30% stanowiły istotne punkty odcięcia charakterystyczne dla przeżycia wg krzywych ROC. U wszystkich chorych zmarłych w mechanizmie SCD zanotowano zwiększoną spoczynkową średnią HR > 78/min. W jednowymiarowej analizie Kaplana-Meiera spośród 27 badanych parametrów wyodrębniono 10 istotnie wpływających na przeżycie (rodzaj profilaktyki, obecność kardiomiopatii, częstoskurczu komorowego, wartość HR, QRS, LVEF, klasa NYHA, ocena DFT, stosowanie statyn i diuretyków pętlowych). W analizie wielowymiarowej metodą Coxa stwierdzono, że ryzyko zgonu zwiększa się przy: średniej wartości LVEF < 30% (3-krotnie), braku oceny DFT (2-krotnie), III, IV klasie wg NYHA (3-krotnie) i niestosowaniu statyn (2-krotnie). Natomiast przeżycie zwiększają: średnia HR < 78/min i szerokość QRS < 118 ms w sposób niezależny od siebie.

Wnioski: W grupie chorych po implantacji ICD w ramach profilaktyki pierwotnej i wtórnej śmiertelność zwiększa się u osób w III, IV klasie wg NYHA, z obniżoną średnią wartością LVEF, u których nie przeprowadzono oceny DFT oraz nie stosowano statyn. U znacznej części tych osób należy rozważać wskazania do resynchronizacji. Zmniejszona HR (normokardia) i wąski zespół QRS stanowią czynniki ochronne w sposób niezależny od siebie. U wszystkich chorych po implantacji ICD w ramach profilaktyki pierwotnej i wtórnej w grupie zmarłych z powodu SCD zanotowano zwiększoną spoczynkową średnią HR. Nie stwierdzono istotnego wpływu utrwalonego migotania przedsionków, interwencji ICD, rodzaju ICD, przeprowadzonych zabiegów rewaskularyzacji mięśnia sercowego na przeżywalność/śmiertelność.

Słowa kluczowe: zgony, ICD, parametry wpływające na przeżycie

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