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LONG-TERM OUTCOMES IN PATIENTS WITH AN IMPLANTED CARDIOVERTER-DEFIBRILLATOR ACCORDING TO THE KUZBASS REGISTRY

<i>Aim</i>	To analyze long-term outcomes by results of the prospective part of the Kuban registry of patients with an implantable cardioverter defibrillator (ICD).
<i>Material and Methods</i>	A prospective analysis of the incidence of hard endpoints and changes in the condition was performed for 260 patients with ICD successively added to the Registry of Patients with Implantable Cardioverter Defibrillator” from 2015 through 2019.
<i>Results</i>	At the time of ICD implantation, all patients had chronic heart failure (CHF), mostly of ischemic etiology with a low left ventricular ejection fraction (LVEF); median LVEF was 30 (25; 36.5) %. 54 of 266 (21.9%) patients died by 2021; 17 of them (31.5%) died in the hospital; in 76.5% of cases, death was caused by acute decompensated heart failure (HF). 139 (53.5%) patients were readmitted; 66 (25.4%) hospitalizations were related with ICDs (lead revision or reimplantation); acute cardiovascular events developed in 38 (14.6%) patients; 12 (4.6%) patients underwent percutaneous coronary interventions; orthotopic heart transplantation was performed for 4 patients. ICD shocks were recorded in 27 (10.4%) patients. After the ICD implantation, median LVEF remained unchanged, 31 (25; 42) vs. 30 (25; 36.5) % ($p>0.05$). However, both objective and subjective HF symptoms worsened. Thus, the number of patients with IIB stage CHF increased from 29.6 to 88.8% ($p<0.01$) and with NYHA III CHF from 24.2 to 34.5% ($p<0.05$). 80 (30.8%) patients visited cardiologists on a regular basis. Only 7.3% of patients received an optimal drug therapy. During the observation period, the rate of beta-blocker treatment considerably decreased, from 90.6 to 64.3% ($p<0.01$), and the rate of the mineralocorticoid receptor antagonist treatment decreased from 50.8 to 17.4% ($p<0.01$). The rate of the diuretic treatment was inconsistent with the severity of patients’ condition.
<i>Conclusion</i>	Most of the problems the patients encountered after the ICD implantation were related with an inadequate treatment of the underlying disease. Since the majority of patients with ICD have a low LVEF, it is essential to focus on prescribing an optimal drug therapy and maintaining compliance with this therapy.
<i>Keywords</i>	Prevention of sudden cardiac death; implantable cardioverter defibrillator; long-term prognosis
<i>For citation</i>	Lebedeva N.B., Talibullin I.V., Parfenov P.G., Kashtalap V.V., Barbarash O.L. Long-term outcomes in patients with an implanted cardioverter-defibrillator according to the Kuzbass registry. <i>Kardiologiia</i> . 2022;62(12):57–63. [Russian: Лебедева Н.Б., Талибуллин И.В., Парфенов П.Г., Кашталап В.В., Барбараш О.Л. Отдаленные исходы у пациентов с имплантированным кардиовертером-дефибриллятором по данным Кузбасского регистра. <i>Кардиология</i> . 2022;62(12):57–63].
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Introduction

Sudden cardiac death (SCD) is an acute problem worldwide, since more than half of patients with cardiovascular diseases die suddenly, and SCD is the first manifestation of the disease in many of them [1]. Up to 80% of SCD cases are associated with coronary artery disease (CAD) due to its high prevalence [2]. There are no official statistics on the SCD in the Russian Federation, but the RESONANCE trial found that the reported annual incidence rate of SCD is 156 per 100 thousand in women and 208 per 100 thousand in men, and the number of SCD cases increases significantly when a clarifying epidemiological coefficient is used [3].

Given that only 5–6% of cases of sudden cardiac arrest occur in hospital, and the prognosis of out-of-hospital cardiac arrest is extremely unfavorable (not more than 10% survival), it is obvious that prophylaxis is the main way to prevent cases of SCD: primary prevention in high-risk groups and secondary prevention after the relevant episode [4, 5]. The use of an implantable cardioverter defibrillator (ICD) is the main method of prevention of SCD in both cases, which is explained by the lack of highly effective and most importantly safe antiarrhythmic drugs [6].

According to one of the Russian studies, the ratio of patients to whom primary prevention of SCD is indicated due to reduced LVEF and patients who had

ICD implanted is 40:1, and the ratio was 8:1 in the case of secondary prevention [7]. In Europe, not more than 60% of need for ICD is covered [8]. The main limitation for the use of ICDs is their high cost, the insufficient number of highly specialized hospitals and specialists providing this type of care. The contributing factor are the limited knowledge about the selection criteria for patients at high risk of SCD among primary care physicians and the lack of effective approved routing schemes for such patients. At the same time, the low demand for ICD therapy is also becoming a real problem, which is associated with ICD pacing failure in a large percentage of patients [9].

Indications for the use of ICD therapy for primary prevention of SCD are based on the results of randomized clinical trials in which reduced LVEF was the main inclusion criterion [10, 11]. ICDs retain positions with a high level of evidence in the updated guideline for the management of chronic heart failure (CHF) [12]. However, it has become increasingly likely that the existing strategy of long-term prevention of SCD based on LVEF as a key criterion for risk stratification is imperfect, including because SCD is associated in the general population not only with reduced LVEF but also with other factors [13].

Moreover, the development of new approaches to pharmacotherapy of CHF contributed to a significant decrease in the incidence of SCD in this category of patients and, consequently, to a decrease in the significance of reduced LVEF as a predictor of SCD [14, 15]. Modern neuromodulatory drugs included in the multicomponent treatment regimen of CHF cause favorable reverse myocardial remodeling and prevent arrhythmogenesis responsible for SCD [16]. On the other hand, the recent results of the EU-CERT-ICD multicenter study showed the benefits of primary preventive ICD therapy with an almost 30% reduction in mortality in the modern cohort of CHF patients [17].

In these circumstances, efforts should be directed at identifying groups of patients who will benefit most from ICD therapy in real-world practice.

Objective

Analyze long-term outcomes in patients with ICD by the results of the prospective part of the Kuzbass Registry of Patients with ICD.

Material and methods

The study was conducted using data from the Kuzbass Registry of Patients with Implantable Cardioverter-Defibrillators, which included 286 patients hospitalized at the Kuzbass Cardiology Center from 2015 to 2019 for the implantation of ICD. The registry was conducted

following the Declaration of Helsinki and was approval by the local ethics committee. All patients signed the informed consent at admission to the hospital. After receipt of the electronic reports of the registry, all patient data were labeled and depersonalized. The registry is a prospective non-randomized observational study of adult patients with a single inclusion criterion, which is the fact of ICD implantation. The follow-up period lasted from two to five years. For the purpose of maintaining the homogeneity of the sample, 22 patients receiving cardiac resynchronization therapy were excluded from the analysis of the prospective stage. We managed to obtain data on the status of being alive or deceased and hard endpoints in 260 the remaining 264 patients by telephone survey and examination of medical records (extracts from hospital charts, outpatient records), 4 patients were lost for observation and regarded as dead. Thus, the analysis of the long-term stage included data on 260 patients with ICD. The follow-up period was 4.6 ± 2.3 years.

Cardioverter-defibrillator was implanted for primary and secondary prevention of SCD following the guideline of the All-Russian Scientific Society of Clinical Electrophysiology, Arrhythmology, and Cardiac Pacing (VNOA), according to which, as well as the guidelines of the European Society of Cardiology, the class of indications for ICD is the IA level in CHF FC II–III (NYHA) and LVEF < 35%, after 3 months of the best possible drug therapy of HF and not earlier than 40 days after myocardial infarction (MI), provided that life expectancy is more than 12 months for primary prevention and there is a history of persistent hemodynamically significant ventricular tachycardia or ventricular fibrillation for secondary prevention of SCD, if radiofrequency ablation is impossible [10, 11]

Clinical data were collected at the inclusion, at certain intervals during follow-up, and entered into a proprietary electronic form [18]. Baseline patient data included demographics, social status, history of underlying disease, comorbidities, vital signs, results of clinical examinations and laboratory tests, doses of cardiovascular drugs, specific parameters related to ICD. Baseline social and demographic characteristics were provided by patients themselves. At the prospective stage, data on changes in patient's condition (HF stage and FC), the frequency of to the cardiologist, arrhythmologist surgeon, the frequency of pacing, and drug therapy were entered in the registry; hard endpoints were recorded: death, hospitalization, acute decompensated heart failure (ADHF), cerebrovascular accident (CVA), acute coronary syndrome (ACS), percutaneous coronary intervention (PCI), coronary angiography (CAG), orthotopic heart transplantation

Table 1. Baseline clinical and anamnestic characteristics of the group

Parameter	n=260
Male, n (%)	214 (82.3)
Age, years	59 (53; 66)
Employed, n (%)	28 (10.8)
CAD, n (%)	194 (74.6)
PICS, n (%)	156 (60)
Noncoronary heart diseases, n (%)	66 (25.4)
AH, n (%)	199 (76.5)
DM type 2, n (%)	34 (13.1)
CKD grade II-III, n (%)	83 (31.9)
COPD, n (%)	23 (8.8)
CCI, n (%)	66 (25.4)
LVEF, %	30 (25;36.5)
AF, all forms, n (%)	106 (40.8)
CHF FC I, n (%)	35 (13.5)
CHF FC IIA, n (%)	147 (56.5)
CHF FC IIB, n (%)	76 (29.6)
CHF FC III, n (%)	2 (0.8)
NYHA FC I, n (%)	4 (1.5)
NYHA FC II, n (%)	175 (67.3)
NYHA FC III, n (%)	63 (24.2)
NYHA FC IV, n (%)	18 (6.9)
Primary prevention of SCD, n (%)	158 (60.8)
Secondary prevention of SCD, n (%)	102 (39.2)
Best possible drug therapy, n (%)	121 (46.5)

Data are presented as the medians and interquartile ranges (Me (25%;75%)), number of patients (n (%)); CAD, coronary artery disease; PICS – postinfarction cardiosclerosis; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; AH, arterial hypertension; DM, diabetes mellitus; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CCI, chronic cerebral ischemia; LVEF, left ventricular ejection fraction; AF, atrial fibrillation; CHF, chronic heart failure; SCD, sudden cardiac death.

(OHT), registration of a new rhythm disorder, revision of the ICD electrode, reimplantation of ICD.

The data were processed using the Statistica 10.0 (StatSoft, USA) and SPSS 10.0 (IBM, USA). The Kolmogorov-Smirnov test was used to determine the normality of distribution. Normally distributed continuous variables were compared using the Student's t-test. Non-normally distributed continuous variables were compared using the nonparametric Mann-Whitney U-test. Discrete variables were compared using the Yates' chi-square test. If there were few patients in a comparison group, the two-sided Fisher test (F-test) was used. The differences were statistically significant with two-tailed $p < 0.05$.

Results

Primary prevention of SCD in patients with reduced LVEF was the main indication for implantation of ICD.

However, chronic heart failure with predominantly reduced ejection fraction (HFrEF) was diagnosed in all patients regardless of the presence of indications for ICD implantation. There were more patients with CHF stage IIA and FC II (NYHA) (Table 1). As can be seen in the table, CAD was the main cause of HF, and more than half of patients had a history of MI. Myocardial revascularization was performed prior to ICD implantation in 135 patients (69.6% of all patients with CAD). Non-coronary diseases, mainly dilated cardiomyopathy, were diagnosed in 25% of patients.

Most patients had comorbidities, arterial hypertension being most prevalent, every third patient had chronic kidney disease, every fourth patient had chronic cerebral ischemia, and chronic obstructive pulmonary diseases and type 2 diabetes mellitus were less common (Table 1). Triple neurohumoral blockade was administered for the treatment of CHF to 121 (46.5%) patients.

Single-chamber and dual-chamber ICDs were implanted in 102 (39.2%) and 158 (60.8%) patients, respectively. All patients were discharged with recommendations for cardiological follow-up, scheduled examination of the ICD by an arrhythmologist in the counseling outpatient clinic in 3 months, and later at least once every 6–12 months, or in case of pacing. Remote monitoring systems were not routinely connected in any of the patients.

During the follow-up period, 54 patients died, i.e. the group mortality rate was 21.9% (including 4 patients with unknown alive/deceased status). These 4 patients were excluded from the follow-up analysis due to the lack of data. A total of 311 endpoints were registered, a mean of 1.2 per patient. Table 2 provides the incidence and structure of the endpoints for the general group and separately for the groups of alive and deceased patients. It is noteworthy that more than half of the patients were hospitalized at least once, and a quarter of hospitalizations were associated with ICD (electrode revision or reimplantation was required); acute cardiovascular events (ACS, CVA, or ADHF) developed in 38 (14.6%) patients. The groups of alive and dead patients did not generally differ in structure and frequency of the endpoints except for the incidence of ADHF and the frequency of CAG.

COVID-19 was diagnosed in 37 (14.2%) patients, of whom 19 (51.4%) patients were hospitalized for COVID-19-related pneumonia.

In the group of deceased patients, 19 (35.2%) patients died in hospital, of whom 3 (17.6%) patients had MI, 1 (5.9%) patients had CVA, 13 (76.5%) patients died of ADHF, and 2 (3.7%) patients died of COVID-19-related pneumonia. 35 (64.8%) patients died outside

the hospital, the main disease declared as the cause of death was dilated cardiomyopathy in 10 (27%) patients, rheumatic mitral valve disease in 1 (2.8%) patients, and the remaining 24 (68.6%) patients died of ischemic cardiomyopathy.

Analysis of changes in patient's condition showed that median LVEF did not change in the general group after implantation of ICD, 31 (25;42) % versus 30 (25; 36.5) % at baseline ($p>0.05$), but was lower in the group of deceased patients (28 (22;34) % versus 33 (26;45) %, $p=0.03$). Objective and subjective symptoms of HF worsened in the follow-up period. The numbers of patients with CHF stage IIB and FC III (NYHA) increased significantly from 29.6% to 88.8% ($p<0.01$) and from 24.2% to 34.5% ($p<0.05$), respectively. The fact that the group of deceased patients was characterized by less pronounced objective and subjective symptoms of HF in lower values of LVEF was unexpected and required more detailed analysis.

The vast majority of patients (204 (78.5%)) visited an arrhythmologist once or twice a year surgeon and 234 (90%) patients were regularly checked up by a primary care physician. Only 80 (30.8%) patients regularly visited a cardiologist. At the same time, only 15 (7.9%) patients in the alive group and 3 (5.65%) in the group of deceased patients received the best possible therapy including triple neurohumoral blockade in the recommended doses.

In the follow-up period, the frequency of administration of renin-angiotensin-aldosterone system inhibitors did not change significantly, the frequency of taking beta-blockers and mineralocorticoid receptor antagonists decreased significantly from 90.6% to 64.3% ($p<0.01$) and from 58.4% to 17.3% ($p<0.01$), respectively. The frequency of diuretic therapy did not increase despite more severe course of CHF, the frequency of taking oral anticoagulants, disaggregants, and statins did not match the number of patients to whom these vital drugs were indicated (Figure 1).

A comparative analysis of the frequency of the administration of drug therapy in the groups of alive and deceased patients showed that deceased patients significantly more often received beta-blockers (88.8% and 59.7%, respectively, $p=0.001$) and diuretics (77.8% and 46.1%, respectively, $p=0.001$), perhaps this fact is associated with better control of CHF severity in this group.

ICD discharges were reported in 10.4% of patients, all from the secondary prevention group (a detailed analysis of pacing is to be carried out in a separate study).

Discussion

Our findings show that the main cohort of patients with ICD, regardless of the type of ICD prevention, is

represented by patients with HFrEF mainly of ischemic origin. Given this fact, it is extremely important to administer the best possible drug therapy for at least 3 months before the implantation of ICD, which is emphasizes in all available guidelines [10, 11]. The best possible drug therapy should include a triple neurohumoral blockade with titration of drugs to target doses, and treatment should be initiated with quad therapy according to the 2021 ESC guideline [12]. Since all guidelines for the use of ICD for primary and secondary prevention of SCD are based on data from studies conducted before 2009, when existing approaches to the treatment of heart failure were immature, new large-scale studies are required to confirm the efficacy of ICD therapy and identify new risk factors and predictors of SCD in the new circumstances [19, 20].

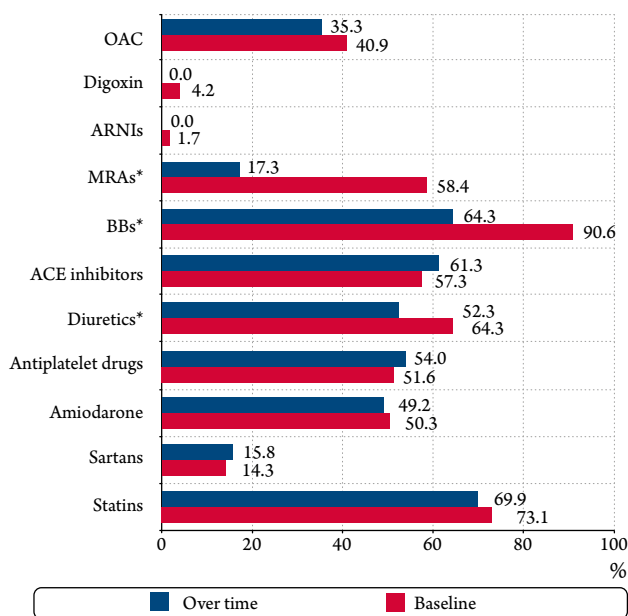
However, our findings reflect the problems of real clinical practice concerning the management and monitoring of such a severe category of patients as HFrEF patients with high risk of out-of-hospital SCD. Similar problems exist not only in Kuzbass but throughout the Russian Federation. According to the EPOCH registry, in 2017, combinations of basic drugs for the treatment of HF FC III–IV (NYHA) used in the Russian Federation included all three recommended groups of drugs only in 14.4%, two drugs in 46.3%, monotherapy in 34.5%, and no treatment in 4.6% of patients [21]. Mortality among patients discharged after an episode of ADHF in the Russian Federation was 25.3%, which is comparable to our findings (21.9%).

The problem of the quality of CHF patients management is worldwide. According to the CHAMP-HF registry, which included a total of 3,518 patients with chronic HFrEF in the United States (mean age 66 ± 13 years, 29% of female patients, mean LVEF $29\pm8\%$), 27%, 33%, and 67% of patients did not receive renin-angiotensin-aldosterone system inhibitors, beta-blockers, and mineralocorticoid receptor antagonists, respectively. Among patients eligible for the administration of all drug classes, only 1% received simultaneously target doses of all three recommended classes of drugs [22].

Thus, the obtained data of real-world clinical practice suggest that the condition of mandatory three-month best possible drug therapy before the implantation of ICD is not met. This fact is of great importance both in terms of understanding the eligibility of patients for ICD implantation and the need for efforts to improve the outpatient management of CHF patients, which can be facilitated by the establishment of CHF centers [23].

Our findings show that the progression of CHF was the main cause of death of patients with ICD. The revealed facts are highly topical, since this situation is observed all

Figure 1. Comparative analysis of the frequency of drug therapy, %



* Differences are statistically significant with $p < 0.05$.
OAC, oral anticoagulant; ARNI, angiotensin receptor-neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist; BB, beta-blocker; ACE, angiotensin-converting enzyme

Table 2. Frequency of the development and structure of endpoints during the follow-up period

Parameter	All patients (n=260)	Alive (n=206)	Deceased (n=54)	P
Hospitalization, n (%)	140 (53.8)	110 (53.4)	30 (55.6)	0.491
Hospitalization related to ICD, n (%)	66 (25.4)	50 (24.3)	16 (29.6)	0.324
ADHF, n (%)	21 (8.1)	7 (3.3)	14 (25.9)	0.001
PCI, n (%)	12 (4.6)	12 (5.8)	0 (0)	0.290
CAG, n (%)	33 (12.7)	29 (14.1)	4 (7.4)	0.043
Reimplantation, n (%)	49 (18.8)	37 (17.9)	12 (22.2)	0.214
Heart transplantation, n (%)	4 (1.5)	3 (1.5)	1 (1.9)	0.870
Electrode revision, n (%)	17 (6.5)	14 (6.8)	3 (5.5)	0.582
Stroke, n (%)	7 (2.7)	6 (2.9)	1 (1.9)	0.767
ACS, n (%)	10 (3.8)	8 (3.9)	2 (3.7)	0.967
New arrhythmia, n (%)	19 (7.3)	16 (7.8)	3 (5.5)	0.473
ICD pacing, n (%)	27 (10.4)	27 (13.1)	Not available	–

The data are presented as the number of patients (n (%)); p is provided for the comparison of alive and deceased patients; ICD, implantable cardioverter defibrillator; ADHF, acute decompensated heart failure; PCI, percutaneous coronary intervention; CAG, coronary angiography; ACS – acute coronary syndrome.

over the world, and mortality of this cohort of patients stays high even with adequate ICD therapy [24]. In addition to the problems related to the management of patients with CHF, the problem of using reduced LVEF as a single predictor of SCD arises. Since all randomized clinical trials with ICD in which LVEF was considered as the only risk criterion were positive, not all the necessary stages were performed to assess reduced LVEF to verify whether it is a sufficient differential discriminating marker [25].

The fact that LVEF is not a highly sensitive and specific predictor of SCD is reflected in the available data that only one-third of patients had reduced LVEF in the population assessment of all cases of LVEF [13]. Patients from the group of the highest ratio of SCD risk/no SCD will benefit the most from ICD therapy, which is why it is important to assess the competing risks of death when indications for ICD therapy are determined. However, current clinical guidelines omit the existing risk of other types of death [26]. Moreover, LVEF may be only partially reproducible when estimated by echocardiography [27]. Given these facts, new markers and strategies for SCD risk stratification are much needed, and, initially, at least the expansion of the range of imaging techniques to assess LVEF [28].

Conclusion

It must be acknowledged that the problem of SCD prevention is far from being solved. There are obviously limitations in the methods of its prevention and the methods of the identification of the category with high risk of SCD to be prevented. Analysis of the registry of patients with ICD revealed the main practical problem associated with ICD therapy, namely, the inconsistency of real-world clinical practice with the available guidelines to meet such an important criterion for the selection of patients for ICD implantation as the administration of the best possible drug therapy and maintaining patient compliance at the outpatient stage.

Limitations

A detailed analysis of the frequency of adequate/inadequate ICD pacing was not performed due to the nature of the registry. Data on ICD pacing were communicated by patients and collected from the arrhythmologist's records.

Funding

No funding was received for this study.

No conflict of interest is reported.

The article was received on 11/03/2022

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