INFLUENCE OF ATRIAL FIBRILLATION ON TWO-YEAR SURVIVAL OF PATIENTS WITH IMPLANTED CARDIOVERTER DEFIBRILLATOR

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Received: 05.02.2022.
Accepted: 19.02.2022.

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UDK: 616.12-085.817"2014/2018"
Eabr 2024; 25(3):259-265
DOI: 10.2478/sjecr-2022-0035

ABSTRACT

Implantable cardioverter defibrillators (ICD) effectively reduce risk of sudden cardiac death in both primary and secondary prevention, but only a small proportion of patients included in the clinical trials had atrial fibrillation. It is still unclear whether patients with atrial fibrillation have the same benefit from ICD implantation as patients in sinus rhythm. This is a clinical, prospective study which included 210 patients in the period 2014-2018. ICD was implanted in the Clinical Center Kragujevac and a two-year follow-up was performed. Patients were divided into 2 groups: a group in sinus rhythm and a group of patients with atrial fibrillation (paroxysmal, persistent and permanent). At the end of the two-year follow-up, there was no difference in survival between the compared groups. The total number of cardioverter defibrillator activations did not differ between the groups, but a significantly higher number of inappropriate cardioverter defibrillator activations was registered in the group with atrial fibrillation. In most patients who had inappropriate defibrillator activation during the two-year follow-up, appropriate defibrillator activation was also registered.

Keywords: *Atrial fibrillation, implantable cardioverter defibrillator, ICD, heart failure, sudden cardiac death.*

INTRODUCTION

Implantable Cardiverter Defibrillator (ICD) is device that is implanted in the patient's body, capable of performing cardioversion, defibrillation and electrostimulation (pacing) of the heart muscle. Today, the use of ICD is the most important primary and secondary prevention of sudden cardiac death (SCD). Primary prevention refers to patients who did not have life-threatening arrhythmia, but based on clinical characteristics, predominantly reduced left ventricular ejection fraction (less than 35%) have an increased risk of life-threatening arrhythmias and SCD. Secondary prevention refers to patients who have previously been successfully resuscitated after cardiac arrest (most commonly caused by ventricular fibrillation) or after life-threatening ventricular arrhythmias, when there is a risk of cardiac arrest recurrence. Large clinical studies have shown superiority of ICD in reducing the incidence of SCD over drug therapy in both primary and secondary prevention (1-5). Atrial fibrillation as the most common arrhythmia is a common comorbidity in patients with reduced left ventricular EF who underwent ICD implantation. Epidemiological studies have shown that atrial fibrillation is associated with increased overall mortality (6), but it is still unclear to what extent it affects mortality in patients with implanted ICD. As one of the potential causes, researchers state a higher frequency of heart failure in the population of patients with atrial fibrillation (7, 8). Heart failure and left ventricular dysfunction affect the development of atrial fibrillation, and atrial fibrillation itself leads to electrical and structural remodeling of the atrial and ventricular myocardium, thus closing the vicious circle. Accelerated heart rate during an atrial arrhythmia, especially in combination with interventricular conduction disorders, may lead to inappropriate activation of the ICD. Inaproppriate ICD activation is device activation and delivery of therapy when there is no life-threatening heart rhythm disorder (e.g. supraventricular arrhythmia or atrial fibrillation) in contrast to appropriate ICD activation. In the MADIT II study 13% of patients with ICD had inappropriate defibrillation shock, where in 44% of cases atrial fibrillation was identified as the main cause (5). Inaproppriate defibrillation shocks as well as appropriate defibrillation shocks may be associated with increased mortality in patients with implanted ICD (9, 10) indicating the need for programming, treatment of underlying disease and heart rhythm disorders to minimize the number of shocks delivered.

Despite the fact that the effective use of ICD devices has been studied in a large number of clinical studies, only a small proportion of patients included in the trials had atrial fibrillation, so it is still unclear whether patients with atrial fibrillation benefit equally from ICD implantation as the patient in synus rhythm.

THE AIM OF THE RESEARCH

To examine whether the presence of atrial fibrillation in patients with implanted cardioverter defibrillators has led to increased mortality and frequency of ICD activation in comparison to patients in sinus rhythm.

PATIENTS AND METHODS

Clinical, prospective study which included 210 patients in the period 2014-2018. who underwent ICD implantation in Clinical Center Kragujevac and had completed two-year follow-up after the implantation. Patients were divided into 2 groups depending on the registered presence of atrial fibrillation. The group of patients with atrial fibrillation consisted of patients who were diagnosed atrial fibrillation (ECG recording of atrial fibrillation lasting minimal 30 seconds), whether paroxysmal, persistent or permanent at any time during follow-up. Group of patients in sinus rhythm consisted of patients without recordings of atrial fibrillalion or other forms of atrial arrhythmias (atrial flutter/atrial tachycardia). All the patients have to meet criteria for ICD implantation (primary or secondary SCD profilaxis). For each ICD implantation, the patient was hospitalized in the Kragujevac Clinical Center, where hospitalization could be elective or urgent. During hospitalization, the following data were collected for each patient: demographic data, risk factors, echocardiographic findings, indications for the implantation of ICD, previous arrhythmic events, associated cardiovascular diseases, lab analysis (blood count, cardiac enzymes, NT-proBNP, CRP, BUN, electrolytes).

ICD device implantation was performed in local anesthesia. Venous approaches were used for placement of electrode catheters: ligation and incision of the cephalic vein or via the subclavian or axillary vein by the puncture method. The positioning of the electrode catheter in the right ventricle was performed under radioscopic control, usually in the interventricular septum or the apex of the right ventricle. The pulse generator is placed subcutaneously prepectorally. Patients who underwent an ICD device implantation came for regular, quarterly check-ups during the next period of 2 years. Exept regular controls urgent or symptom driven check-ups of the petents were also recorded. The following data were collected each time the patient arrived: ICD device function parameters, recorded arrhythmic events, data on the patient's subjective sympthoms, findings of subsequent diagnostic and therapeutic procedures. Controls of ICD devices are performed with the help of appropriate programmers of device manufacturers. All data obtained during the control examination were recorded in the patient's card and in electronic form. In case of absence of follow-up examinations patient data were obtained by telephone or by insight in the hospital's electronic information system.

In the statistical analysis we used descriptive methods and methods of analytical statistics.To compare the categorical variables we used Chi square test. For the analysis of numerical variables T test or Mann-Whitney test were used. In order to assess the survival between different groups of patients, we used Kaplan-Maier curve and Log-rank test.

RESULTS

The study included 210 patients (47,1% in sinus rhythm and 52.9% in the atrial fibrillation). Demographic characteristics of the groups are shown in Table 1.

Table 1. Demographic characteristics of patient groups

Group		Sinus rhythm	Atrial fibrillation	p
Number(%)		99 (47,1%)	111 (52,9%)	
Age (years)		67,7 ± 11,3	67,7 ± 9,6	p=0,517[a]
Gender	Man	68 (68,7%)	78(70,3%)	p=0.062[b]
	Woman	31 (31,3%)	33 (29,7%)	
Hypertension		77,8%	88,3%	p=0.064[b]
Diabetes mellitus		41,4%	28,8%	p=0.056[b]
Hyperlipidemia		65,6%	60,0%	p=0.399[b]
Smoking		27,3%	21,6%	p=0.340[b]
Heredity		27,2%	21,6%	p=0.340[b]
[a] T test, [b] Xi square test, * significance level 0.05				

The groups did not differ statistically significant according to the age of the patients, gender, nor the presence of risk factors. There is trend of higher prevalence of diabetes mellitus in the sinus rhythm group, but statistical significance has not been achieved.

The values of laboratory parameters monitored in patients are shown in Table 2.

Table 2. Value of laboratory parameters between compared groups

Group		Sinus rhythm	Atrial fibrillation	p
NT-proBNP (pg/mL)	Mean ± SD	4037.5 ± 5474.5	4852.3 ± 6645.1	p=0.177[c]
	Median	1519.5	2036	
Troponin (pg/mL)	Mean ± SD	0.065 ± 0.138	0.065±0.20	p=0.978[c]
	Median	0.019	0.019	
Hemoglobin (g/L)	Mean ± SD	125.1 ± 18.5	129.4 ± 22.9	p=0.113[c]
	Median	129	132	
CRP (mg/L)	Mean ± SD	8.39 ± 12.28	8.33 ± 10.8	p=0.815[c]
	Median	4.95	4.20	
Urea (mmol/L)	Mean ± SD	9.00 ± 4.01	8.38 ± 4.25	p=0.362[c]
	Median	8.15	7.6	
Creatinine (µmol/L)	Mean ± SD	125.9 ± 157.5	114.1 ± 52.0	p=0.104[c]
	Median	96	104	
Na^+ (mmol/L)	Mean ± SD	139.6 ± 3.8	135.42 ±14.25	p=0.794[c]
	Median	140	140	
[c] Mann-Whitney test * significance level 0.05				

The values of laboratory parameters: NT-proBNP, troponin, hemoglobin concentrations, CRP, urea, creatinine and serum sodium ion concentrations did not differ significantly between the compared groups. The prevalence of cardiovascular drug therapy is shown in Table 3.

Table 3. Prevalence of cardiovascular drug groups in patient groups.

Group	Sinus rhythm	Atrial fibrillation	p
Amiodarone	**49.5%**	**68.5%**	**p=0.005[b*]**
Beta blocker	84.5%	91.0%	p=0.154[b]
ACE inhibitor	74.7%	71.2%	p=0.481[b]
Anticoagulant therapy	**61.0%**	**95.5%**	**p=0.000[b*]**
ASA	**56.1%**	**25.2%**	**p=0.000[b*]**
Thienopyridine	**19.1%**	**9.0%**	**p=0.028[b*]**
Statin	67.7%	58.6%	p=0.143[b]
[b] Xi square test, * significance level 0.05			

A statistically significantly higher prevalence of amiodarone was observed in atrial fibrillation group in comparison to sinus rhythm group (p = 0.005). Patients with atrial fibrillation had a statistically significantly higher prevalence of oral anticoagulant drugs in therapy, while patients with sinus rhythm had a statistically significantly higher prevalence of antiplatelet drugs (ASA and thienopyridines) (p=0.000).

Out of the total number of patients, 46.5% (99 patients) had myocardial disease of ischemic etiology, while 53.5% of patients (111 patients) had non-ischemic etiology of heart disease. The prevalence of associated cardiovascular diseases between the compared groups is shown in Table 4.

Table 4. Prevalence of associated cardiovascular diseases.

Group	Sinus rhythm	Atrial fibrillation	p
Ischemic heart disease	**60.6%**	**35.1%**	
Non-ischemic heart disease	**39.4%**	**64.9%**	**p=0.000[b*]**
Peripheral artery disease	**21.2%**	**9.9%**	**p=0.023[b*]**
Cerebrovascular event	**5.0%**	**14.4%**	**p=0.024[b*]**
Chronic renal failure	7.1%	10.8%	p=0.346[b]
[b] Xi square test, * significance level 0.05			

Myocardial disease of ischemic etiology and peripheral artery disease were significantly more prevalent in the group of patients in sinus rhythm compared to atrial fibrillation group. The group of patients with atrial fibrillation had a significantly higher number of patients who had cerebrovascular event, compared to sinus rhythm group, as well as a significantly higher number of patients with non-ischemic etiology of heart muscle disease.

At the end of the two-year follow-up 89.9% of patients in the sinus rhythm group and 91.0% of patients with atrial fibrillation were alive. There was no statistically significant difference in patient survival between the compared groups during the two-year follow-up of patients (Log rank, p = 0.785). Patient survival curves are shown in Figure 1.

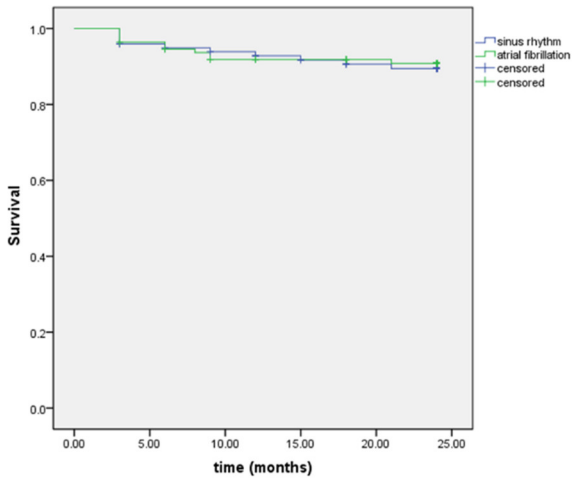


Figure 1. Patient survival curves.

During a two-year follow-up of a total of 210 patients enrolled in the study, 39 patients (18.3%) had activation od ICD in the form of antitachycardia pacing and/or defibrillation shock. Table 5. shows the distribution of patients with ICD activation between the groups.

Table 5. Distribution of patients with ICD activation between the compared groups.

Group	Sinus rhythm	Atrial fibrillation	p
Number of patients with ICD activation	16 (16.2%)	23 (20.7%)	P=0.396[b]
[b] Xi square test, * significance level 0.05			

There was no difference in the number of ICD activation between the compared groups at the end of the two-year follow-up.

Out of total of 39 patients in whom ICD activation occurred during the two-year follow-up, in 25 patients (64.1%) the appropriate ICD activation was registered. In 14 patients (35.9%), inappropriate activation of the ICD was registered. Appropriate and inappropriate defibrillation shock may be reported in same patients during follow-up. Figure 2 shows the types of activation of the ICD during the two-year follow-up.

Most patients with ICD activation had appropriate ICD therapy. In patients who had inappropriate therapy in most cases during two-year follow-up in addition to inappropriate an appropriate ICD therapy was registered. Distribution of ICD activation types between the groups was shown in Table 6.

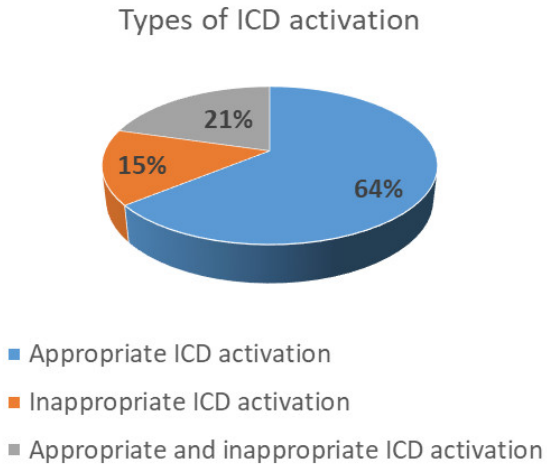


Figure 2. Types of activation of the implanted cardioverter defibrillator.

Table 6. Distribution of types ICD activation between the groups.

Group	Sinus rhythm	Atrial fibrillation	P
Incidence of appropriate ICD activation	16 (48.5%)	17 (51,5%)	p=0.863[b]
Incidence of inappropriate ICD activation	**3 (21,4%)**	**11 (78,6%)**	**P=0.046[b*]**

There was no difference between compared groups in the number of patients with appropriate activation of ICD. The group of patients with atrial fibrillation had significantly more patients with inappropriate ICD activation compared to the sinus rhythm group (p=0.046).

DISCUSSION

Out of the total number of patients included in the investigation, 52,9% had atrial fibrillation (paroxysmal and permanent), while 47,1% of the patients were in sinus rhythm. The prevalence of atrial fibrillation in our investigation can be compared with study of authors from Leiden (11) which included 913 patients (27% with atrial fibrillation: paroxysmal, persistent, permanent) followed for an average of three years after ICD implantation. This study revealed higher mortality of patients with permanent atrial fibrillation compared to patients in sinus rhythm (35% vs. 12%), while patients with paroxysmal and persistent atrial fibrillation had similar mortality compared to patients in sinus rhythm. Patients with permanent atrial fibrillation in this study had significantly higher NYHA class of heart failure, lower creatinine clearance, wider QRS complexes, more frequent use of antiarrhythmics and diuretics than sinus rhythm group, which points association between patients risk profile and survival rather than the impact of atrial fibrillation itself. The presence of ischemic heart disease was more common in patients with sinus rhythm, paroxysmal and persistent atrial fibrillation, while the presence of non-ischemic heart disease was more common in the permanent atrial fibrillation group, similar to our research. In our study, there was no difference in mortality between the groups, but there was no difference in the risk profile that existed in the Leiden study. Investigators from Leiden have included patients in the study since 1996, while our study included patients who had an ICD implanted since 2014. so it should be taken into consideration that significant progress has been made in the treatment of heart

failure in recent years which could improve survival of the patients.

In the MADIT II study (12) patients with atrial fibrillation accounted for only 8% of patients (102 patients) and had significantly higher risk profile than sinus rhythm patients: elderly patients, higher incidence of chronic renal failure, wider QRS complex, higher NYHA class of heart failure. After twenty months follow-up patients with atrial fibrillation had higher cumulative frequency of hospitalizations and mortality compared with patients in sinus rhythm, noting that the presence of atrial fibrillation was not in itself an independent predictor of increased mortality, but affected more frequent hospitalizations. Sub-analysis of the MADIT II study (13) identified risk factors which reduced the benefit of ICD in reducing SCD such as: advanced age (over 70 years of age), severe heart failure, presence of chronic renal failure, presence of atrial fibrillation and wider QRS complexes. In our trial risk profile did not differ significantly between patient groups (exept higher serum concentration of NT-proBNP in patients with permanent atrial fibrillation), which may explain the equally two-year survival in all patient groups.

Sub-analysis of another important study which examined the optimal programming of ICD algorithms (PREPARE study), assesed the impact of atrial atrial fibrillation/tachycardia on mortality and ICD function (14). After one year follow-up 8% patients experienced ICD shock with higher number of ICD shocks in patients with atriall fibrillation and inappropriate shocks accounting for the majority of the difference (6.9% vs 2.6%, P = 0.02), but the mortality was similar in patients with and without atrial fibrillation/tachycardia.

In accordance with the current recommendations for the treatment of heart failure, most patients in our study were treated with beta-blockers, statins and ACE inhibitors. There was no statistically significant difference in the prevalence of these drugs between the compared groups of patients. Prevalence of amiodarone was significantly higher in the group of patients with paroxysmal and permanent atrial fibrillation compared to patients in sinus rhythm, which can be explained by strategy of rate and rhythm control, beside its use to suppress ventricular arrhythmias in both groups. According to the recommendations for the treatment of atrial fibrillation, use of anticoagulant therapy in order to reduce ischemic thromboembolic events is the basis of treatment. As the patients with atrial fibrillation included in our investigation were already with significant structural myocardial disease, even without the presence of other risk factors they had elevated CHA2DS-VA2SC score which justifies anticoagulant therapy.

As the presence of atrial arrhythmias may be one of the reasons for inappropriate activation of ICD devices, in our study we examined the causes that led to device activation and delivery of therapy, based on which we classified the delivered antitachycardia therapy as appropriate and inappropriate. During the two-year follow-up of patients with ICD in our study, out of the total number of patients who had ICD activation and delivery of antitachycardia therapy, 36% of patients had inappropriate device activation. There was no statistically significant difference in the number of patients with appropriate ICD activation between the groups, but in the group of patients with atrial fibrillation in our study we observed significantly higher number of patients with inappropriate ICD activation and defibrillation shock delivery (11 patients versus 3 patients). In the already mentioned Leiden group study (15), during three-years follow-up there was singifficantly higher number of patients with inappropriate ICD activations in permanent atrial fibrillation group (32% of patients) and paroxysmal atrial fibrillation group (28% of patients) in comparisson sinus rhythm group (13% of the patients). This trial has also reported higher inicedence of appropriate ICD activations in the permanent atrial fibrillation group in comparison to other forms of atrial fibrillation and to sinus rhythm group, which could be attributed to higher risk profile of patients and more severe form of heart failure in this group.

Higher rate of inappropriate defibrillator activations in patients with atrial fibrillation in our investigation could be explained by the effort to keep patients with paroxysmal atrial fibrillation in sinus rhythm for as long as possible, but also to feel good in daily activities, which affects the choice and dose of antiarrhythmic drugs. In patients with atrial fibrillation, attacks of paroxysmal atrial fibrillation, even in the short term, could lead to an acceleration of the heart rate, entry into the ICD therapeutic zone and delivery of antitachycardia therapy. In our study, we found that the majority of patients (57%) who had inappropriate ICD activation and defibrillation shock delivery had also appropriate defibrillator activation during the two-year follow-up, which may explain the fact that there was no difference in morality between the compared patient groups. Patients in whom inappropriate activation of ICD devices occurred in most cases benefited from implantation because they also had appropriate defibrillator activations which interrupted life-threatening heart rhythm disorders.

CONCLUSION

1. In patients with ICD, there was no statistically significant difference in mortality after two years follow-up between patients with atrial fibrillation and patients in sinus rhythm.

2. In patients with ICD, there was no statistically significant difference in the number of patients with activation of ICD after two years follow-up between patients with atrial fibrillation and patients in sinus rhythm.

3. During the two-year follow-up of patients with ICD, inappropriate activation of the ICD was registered in 36% of patients who had activation of ICD. There was significantly higher number of patients with inappropriate ICD activation in patients who had atrial fibrillation compared to patients in sinus rhythm.

4. The majority of patients (57%) who had inappropriate activation of the ICD and delivery of defibrillation shock, also had appropriate ICD activation during the follow-up.

CONFLICT OF INTEREST

The authors declare no financial or commercial conflict of interest.

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