Different arrhythmic prognosis in high-risk arrhythmogenic right ventricular cardiomyopathy according to the indication of the defibrillator

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Abstract

Background: Arrhythmogenic right ventricular cardiomyopathy (ARVC/D) is an inherited cardiomyopathy characterized by ventricular arrhythmias and heart failure. The aim of our study was to analyze the impact of the ICD indication in the prognosis of patients with high-risk ARVC/D according to the consensus document.

Methods The high-risk category includes patients who experienced cardiac arrest due to sustained ventricular tachycardia or ventricular fibrillation and patients with severe right or left ventricular dysfunction. We included 41 patients with high-risk ARVC/D: 33 in secondary prevention and 8 in primary prevention.

Results We followed 41 patients during 6.37 ± 4.88 years. Twenty-six patients (63.4%) had at least one appropriate arrhythmic event: 24 p (72.7%) in secondary prevention and 2 p (25%) in primary prevention; p=0.02. Twenty-four patients (72.7%) in secondary prevention and five (62.5%) in primary prevention had a cardiovascular event such as arrhythmias, admission due to heart failure, heart transplantation or cardiovascular death.

Conclusions High-risk ARVC/D patients had a high number of cardiovascular events, but their nature and treatment were different. Arrhythmic prognosis was worse in secondary prevention and most of the events found in primary prevention were related to heart failure and, therefore, without benefit of the ICD.

Background

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is an inherited cardiomyopathy characterized by fibrofatty replacement of predominantly the right ventricular (RV) myocardium. These structural alterations can lead to sudden cardiac death (SCD) and heart failure [1–4].

For ethical reasons there are not prospective randomized trials and the observational clinical studies have provided clinical predictors of outcome including arrhythmic events, heart transplantation or death. There are an international consensus document[5] and a clinical practice guideline [6] to help us select the patients who benefit from the implantable cardioverter-defibrillator (ICD). Patients at increased risk of arrhythmic events are those who have already presented a sustained ventricular arrhythmia or sudden death, with a class I indication.

The problem is in primary prevention, where the risk estimation and recommendations are different. The consensus estimates high risk for patients with ARVC/D who have severe RV or left ventricular (LV) dysfunction with an estimated annual arrhythmic event > 10%/year, so the ICD must be implanted with a class I recommendation [5]. Otherwise, the guideline only gives class IIb indications in primary prevention with one or more risk factors, the most powerful being unexplained syncope [6].

Because of these discordant data, the aim of our study was to analyze the impact of the ICD indication in the prognosis of 41 patients with high-risk ARVC/D according to the consensus document.

Methods

1. Study design and population

This observational retrospective cohort study included 41 patients from 6 different hospitals in southern Spain diagnosed with high risk ARVC/D between January 1996 and January 2017 who were followed in an arrhythmia unit after the implantation of the ICD.

Diagnosis was established in accordance with revised 2010 Task Force criteria, included patients with definite (2 major or 1 major and 2 minor criteria or 4 minor criteria from different categories) and borderline (1 major and 1 minor or 3 minor criteria from different categories) ARVC/D [3].

The high-risk category includes patients who experienced cardiac arrest due to sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) and patients with severe RV dysfunction (RV fractional area change ≤17% or RV ejection fraction (RVEF) ≤35%) or severe LV dysfunction (LV ejection fraction (LVEF) ≤35%) even without arrhythmic events [5].

Demographic, clinical, genetics, electrocardiographic and arrhythmic characteristics were recorded at the time of diagnosis. RV and LV function was estimated by echocardiogram (RV fractional area change and LV ejection fraction) or cardiac resonance (LV ejection fraction and RV ejection fraction).

All the patients were implanted with a single-chamber ICD programmed with one (VF>200–220 bpm) or two detection zones (VT at rates between 170–200 bpm with discrimination algorithms and VF>200 bpm).

2. Follow-up

During follow-up, we recorded arrhythmic events (appropriate and inappropriate); the incidence of heart failure, ablation, deaths and heart transplants that occurred.

Appropriate events were defined as intervention by the ICD with anti-tachycardia therapy (ATP) or shocks in response to sustained ventricular arrhythmia. Inappropriate events were defined as ATP or shock for non-ventricular tachycardia (supraventricular tachycardia or device malfunction). All stored electrograms of arrhythmic events that triggered ICD therapy were classified as appropriate or inappropriate by 2 experienced electrophysiologists. Ventricular tachycardia storm was defined as 3 or more clusters of multiple, consecutive appropriate discharges within 24 hours.

3.Statistical analysis

The SPSS (version 18.0) programme was used for data analysis. Continuous variables are expressed as a mean ± typical deviation and categorical variables as an absolute value and a percentage. For the

comparison of continuous variables, Student's t test was used (in the case of normal distribution) or Mann-Whitney U (for those that did not have a normal distribution). Categorical variables were compared by means of contingency tables and the application of the $\chi 2$ test or Fisher's exact test. The study of appropriate arrhythmic event-free time and heart failure event-free were performed using the Kaplan Meier method.

A two-tailed value of $p<0.05$ was considered statistically significant.

Results

- Baseline characteristics of the sample

The majority were male (32 patients, 78.05%) with a mean age on diagnosis of 46.8 ± 17.5 years. Thirty-six patients (87.8%) had definite ARVC/D and the remaining 5 (12.2%) were borderline according to the Task Force criteria modified in 2010.[3] The diagnostic criterion for each patient is shown in detail in Table 1.

Regarding clinical presentation, 33 patients were diagnosed based on arrhythmic events (secondary prevention): two patients suffered an aborted SCD and thirty-one had sustained VT with left bundle branch block morphology (22 superior axis and 9 inferior axis). Eight patients had a primary prevention ICD due to severe ventricular involvement (2 biventricular and 6 right ventricular): four were diagnosed from a study for ventricular extrasystole, three during a study for dyspnea with heart failure and other during a familial screening.

A pathogenic or probably pathogenic desmosomal mutation was detected in 26 of 35 patients with a genetic test. Of these mutations, plakophilin–2 was the most frequent with nineteen variations, followed by desmoglein–2 with five and desmoplakin with three.

The mean LVEF was 57.9 ± 9.5%, seven patients (17.1%) had LV involvement and two of them (4.9%) presented severe ventricular dysfunction (LVEF≤35%). Late gadolinium enhancement was present in 12 of the 20 patients who underwent cardiac magnetic resonance. The mean RVEF was 39.4 ± 17.4% measured by resonance and 20 patients suffered severe RV dysfunction (fractional area change ≤17% or RVEF≤35%).

Eighteen patients (43.1%) were athletes before the diagnosis. The exercise was not associated to differences with the indication of the ICD (48.5% in secondary prevention and 25% in primary, $p = 0.2$), but the athletic patients were younger at the time of diagnosis (33.3 ± 11 years vs 55.2 ±14 years, $p<0.001$).

All patients underwent beta-blockers from the diagnosis and the follow-up. Fourteen patients (34.14%) had taken amiodarone, none before the first arrhythmic event.

- Arrhythmic events

During a mean follow-up of 6.37 ± 4.88 years, 26 patients (63.4%) had at least one appropriate arrhythmic event. The mean time to onset of the first event was 11.42 ± 9.1 months.

A total 364 ventricular arrhythmias with a mean cycle length of 278.5 ± 38.68 ms were recorded and treated. The effectiveness of anti-tachycardia pacing (ATP) was high: 324 (89.01%) reverted with ATP, while the rest required shocks: 40 episodes in 15 patients (36.59%). Nine (21.95%) were admitted for arrhythmic storm and seven (17.07%) required substrate ablation for repetitive ventricular arrhythmias.

Table 2 shows the baseline characteristics at the time of diagnosis and the arrhythmic events in the follow-up according to the indication of the ICD.

Arrhythmic prognosis was worse in secondary prevention than in primary prevention with more affected patients (24p (72.7%) vs 2p (25%); p = 0.02), and also with a nonsignificant tendency to a greater arrhythmic storms (8p (24.2%) vs 1p (12.5%); ns) and ablations (6p (18.2%) vs 1p (12.5%); ns). The lower free survival arrhythmic event is shown in figure 1.

All the appropriate events were by VT in primary prevention. In secondary prevention, the majority were by VT, but 2.3% (8/350 events) were by VF. There were no deaths of arrhythmic origin.

The severe involvement of the RV (fractional area change ≤17% or RVEF ≤35%) was not associated with a lower survival free of arrhythmic events as shown in figure 2.

Five patients suffered inappropriate shocks during follow-up: three due to atrial fibrillation, one due to sinus tachycardia and other due to noise after the fracture of the electrode.

- Non-arrhythmic events

During follow-up, 5 patients (12.2%) were admitted due to heart failure, 2 patients had a heart transplant for refractory heart failure, there were no cardiovascular deaths and 2 died because of non-cardiac causes: one due to pneumonia and the other due to cancer.

Severe RV involvement (fractional area change ≤17% or RVEF ≤35%) was associated with an increased risk of non-arrhythmic events such as heart failure admissions (5p (25%) vs 0%, p = 0.02) and heart transplant (2p (10%) vs 0; ns).

Three patients had complications related with the device: two infections and an electrode fracture.

- Total events

During follow-up, after the implantation of the ICD, 29 patients (70.73%) presented a cardiovascular event such as ventricular arrhythmias, hospitalization due to heart failure, heart transplantation or cardiovascular death.

Comparing the primary and secondary prevention groups with respect to the risk of any cardiovascular event, there were no differences as shown in figure 3: 24 patients (72.7%) in secondary prevention and 5 patients (62.5%) in primary prevention had cardiovascular event.

Discussion

The data obtained in our study suggest that patients with high-risk ARVC/D have a high number of cardiovascular events, but their nature and treatment are different. Patients with ICD in secondary prevention presented more risk of arrhythmic events (72.7%) and, therefore, are the ones that would benefit more from the implantation of the ICD and should have a greater degree of recommendation in the guidelines and in the consensus document (class I).

The incidence of arrhythmic events in primary prevention was significantly lower (25%) and this suggests that the indication of ICD in primary prevention could have a lower power or level of recommendation than in secondary prevention, but we need more studies, with a greater number of patients that provide us with more information in the future. These patients had a higher number of cardiovascular overall (62.5%) which indicates the risk profile of events, but its features are heterogeneous, most of them related to heart failure and, therefore, not treatable with the ICD.

The selection of patients for ICD implantation in primary prevention is very difficult, as the data that associates severe ventricular involvement with a worse prognosis are based on small retrospective series. The ITF consensus documentassigns high risk to patients without prior ventricular arrhythmias who present severe LV or RV dysfunction with a Class I indication for ICD implantation [5]. This indication is based on “personal experience and extrapolation of other cardiomyopathies” and principally on three publications.

In 2004, Wichter et al. [7] published a follow-up of 60 ARVC/D patients with an ICD, 93% in secondary prevention and 7% in primary prevention, who had had sustained monomorphic VT induced during the electrophysiology study and had a first degree family history of sudden death. They concluded that RV dysfunction is independently associated with appropriate events during the follow-up. These patients had, by definition, high arrhythmic risk as 93% of them had already had a major arrhythmic event that justified the implantation of an ICD.

Saguner et al. [8] published a follow-up of 70 ARVC/D patients (76% were definite), 60% had prior ventricular arrhythmias (3% with SCD and 57% with sustained monomorphic VT), and they studied the cardiovascular composition including heart transplant and ventricular arrhythmia. The RV fractional area change and tricuspid annulus plane systolic excursion parameters related to RV dysfunction were associated as predictors of cardiovascular events, but of the 32 patients with recorded arrhythmic events, 31 had appropriate ICD events, and without specifying whether these were in primary or secondary prevention, it seems clear that they were high risk. This study made no comparison of the recorded events between primary and secondary prevention.

Finally, in a registry of a 10-year follow-up, Pinamonti et al. [9] followed 96 ARVC/D patients and independently associated severe involvement of the right ventricle with a bad cardiovascular prognosis, defined as death or transplant. The profile of these patients was low-risk (27% asymptomatic, 41% palpitations, 15% syncope, 3% aborted SCD) and 20 of them suffered major cardiovascular events, most of which were associated with heart failure (seven transplants for heart failure, six deaths for heart failure refractory to treatment, six for sudden death and another to unknown causes). Additionally, only twelve patients had an ICD (nine for secondary prevention) and only three presented appropriate events during follow-up.

Recently, Kimura et al. [10] published a study with the difference regarding gender in the presentation of the disease; male patients had a significantly higher risk of ventricular arrhythmias, whereas female patients had a significantly higher risk of heart failure death or heart transplantation. A lower RVEF was associated with a higher probability of heart failure but not of ventricular arrhythmias and this heart failure hospitalization had a significant relation with malignant clinical course [11].

ARVC/D is most commonly transmitted as an autosomal dominant trait with incomplete penetrance and variable and age-dependent clinical expression [12,13]. Knowledge of the genetic and pathophysiology of ARVC/D can help in its early diagnosis and in the detection of factors associated with events in primary prevention. Castelletti et al associated missense and non-missense desmoplakin mutations with an increased arrhythmic [14], but studies are still needed to provide more information on the factors associated with arrhythmic events in primary prevention of ARVC/D.

Limitations

The main limitation is that the study population is small (41 patients) and the results obtained, although with significant differences and congruent with previous studies, should be taken with caution.

Other limitations are the retrospective nature of the study, the possible influence of the exercise on the results and the absence of high-risk patients without ICD.

Conclusions

Our results support the classification of the guidelines in high-risk ARVC/D patients because they had a high number of cardiovascular events (70.73%) such as ventricular arrhythmias, hospitalization due to heart failure or heart transplantation, but their nature and treatment were different.

Arrhythmic prognosis was worse in secondary prevention and these patients benefited more from the ICD. Most of the events found in primary prevention were related to heart failure and, therefore, without benefit of the ICD. Primary prevention studies are still needed to provide more information on the factors associated with arrhythmic events in ARVC/D.

Declarations

Ethics approval and consent to participate: The study was approved by the Institutional Committee on Human Research at the authors' institution and complies with the 1975 Declaration of Helsinki ethical principles.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: ARS (the principal investigator) has designed the study with input from ISN, CMP, ABC, MJN, ERC, JMGP, FCB, LMH, JJGD and JA. ISN, MJN, JMGP, FCB, LMH and JJGD are responsible for recruitment and follow-up. ARS, CMP, ABC and JA are responsible for ICD implanting.

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Tables

Table 1. Task Force criteria for ARVC/D diagnosis 2010 of the study patients: 36 definite ARVC/D and 5 borderline ARVC/D.

Patient	Major/minor criteria	Structural alterations	Repolarization abnormalities	Depolarization abnormalities	Arrhythmias	Family history and genetic
1	2/2	minor	Major	-	minor	Major
2	3/0	Major	-	-	Major	Major
3	3/0	Major	-	-	Major	Major
4	5/0	Major	Major	Major	Major	Major
5	4/0	Major	Major	-	Major	Major
6	3/1	Major	Major	-	minor	Major
7	4/0	Major	Major	-	Major	Major
8	3/1	minor	Major	-	Major	Major
9	4/0	Major	Major	-	Major	Major
10	3/1	Major	Major	-	minor	Major
11	4/1	Major	Major	Major	minor	Major
12	3/1	Major	Major	-	minor	Major
13	4/1	Major	Major	Major	minor	Major
14	5/0	Major	Major	Major	Major	Major
15	3/1	Minor	Major		Major	Major
16	3/0	Major	-	Major	Major	-
17	3/0	-	Major	-	Major	Major
18	3/0	Major	Major	-	Major	-
19	4/1	Major	Major	Major	minor	Major
20	2/2	minor	Major	-	minor	Major
21	2/2	minor	minor	-	Major	Major
22	4/0	Major	-	Major	Major	Major
23	2/2	minor	minor	-	Major	Major
24	2/2	Major	minor	-	minor	Major
25	4/1	Major	Major	Major	minor	Major
26	3/2	Major	Major	minor	minor	Major
27	2/0	Major	-	-	Major	-
28	3/0	Major	Major	-	Major	-
29	4/0	Major	Major	Major	Major	-
30	2/1	-	minor	Major	Major	-
31	1/2	minor	Major	-	minor	-
32	1/2	Major	minor	-	minor	-
33	5/0	Major	Major	Major	Major	Major
34	3/1	Major	Major	-	minor	Major
35	3/1	Major	Major	-	minor	Major
36	2/1	Major	Major	minor	-	-
37	1/1	Major	minor	-	-	-
38	1/1	Major	-	-	minor	-
39	1/1	Major	-	-	minor	-
40	1/1	minor	-	-	Major	-
41	1/1	minor	-	-	Major	-

Table 2. Baseline characteristics of patients at the time of diagnosis and the arrhythmic events in the follow-up according to the indication of the ICD (primary and secondary prevention). LVEF: ejection fraction of left ventricle; Severe RV dysfunction: fractional area change ≤17% or ejection fraction of right ventricle ≤35%).

Clinical characteristics	Primary prevention (n= 8)	Secundary prevention (n=33)	p
Age at diagnosis (years)	50.3 ± 14.1	45.6 ± 18.5	0.19
Male gender, n (%)	4 (50%)	27 (81.8%)	0.08
Definite ARVC/D, n (%)	6 (75%)	30 (90.9%)	0.25
Genotype positive, n (%)	4 (50%)	23 (69.7%)	0.23
Severe RV dysfunction, n (%)	**8 (100%)**	**12 (36.4%)**	**0.01**
LVEF (%)	53.6 ± 11.5	59 ± 8.9	0.29
Atrial fibrillation, n (%)	2 (25%)	6 (19.4%)	0.59
Appropriate arrhythmic event, n (%)	**2 (25%)**	**24 (72.7%)**	**0.02**
Number of sustained VT, n	**14**	**350**	**0.001**
VT storm, n (%)	1 (12.5%)	8 (24.2%)	0.42
VT ablation, n (%)	1 (12.5%)	6 (18.2)	0.55

Figures

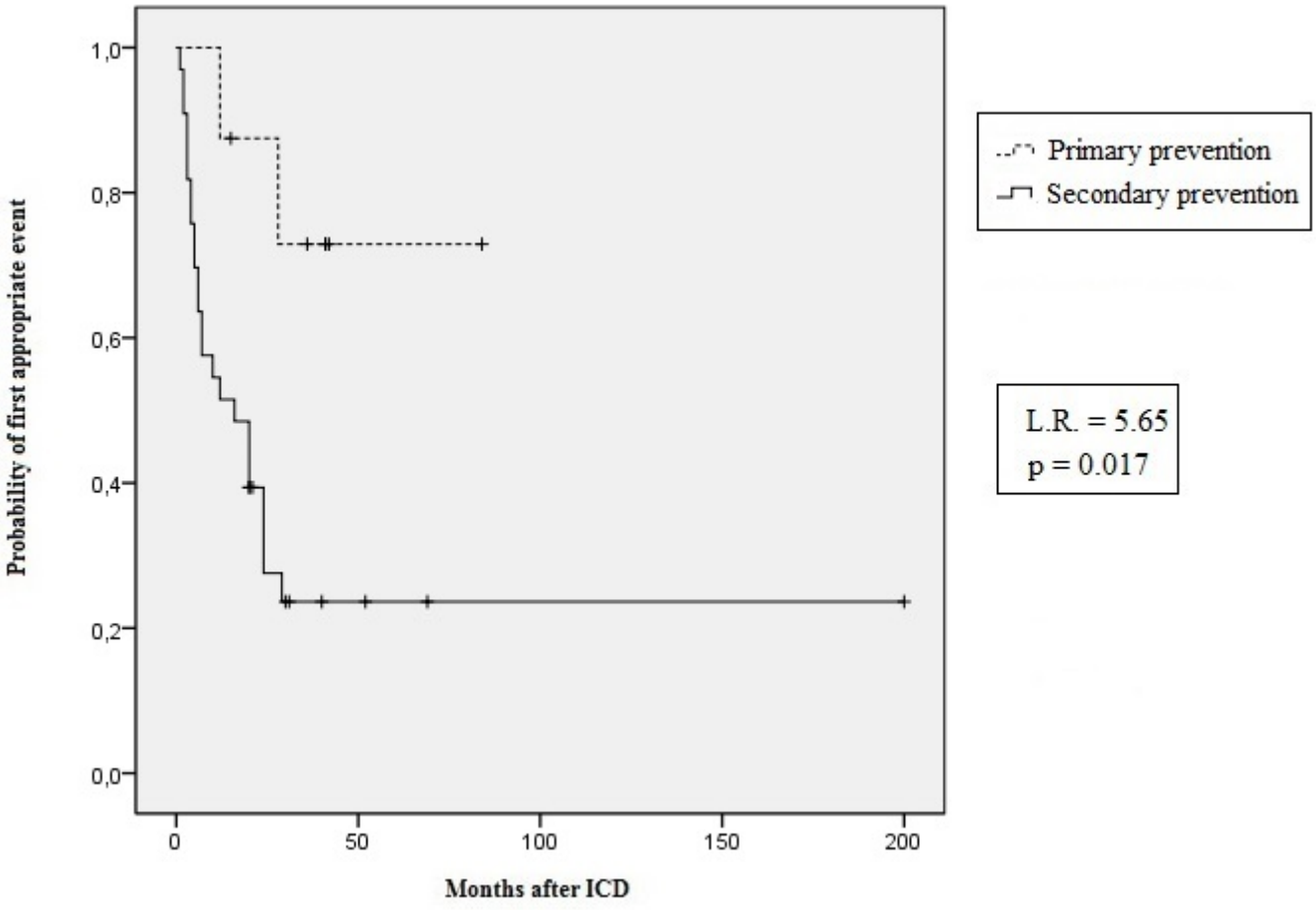

Figure 1

Kaplan-Meier graph showing the cumulative probability of the first appropriate arrhythmic event by the ICD according to the indication of the ICD (primary and secondary prevention). ICD: implantable cardiac defibrillator.

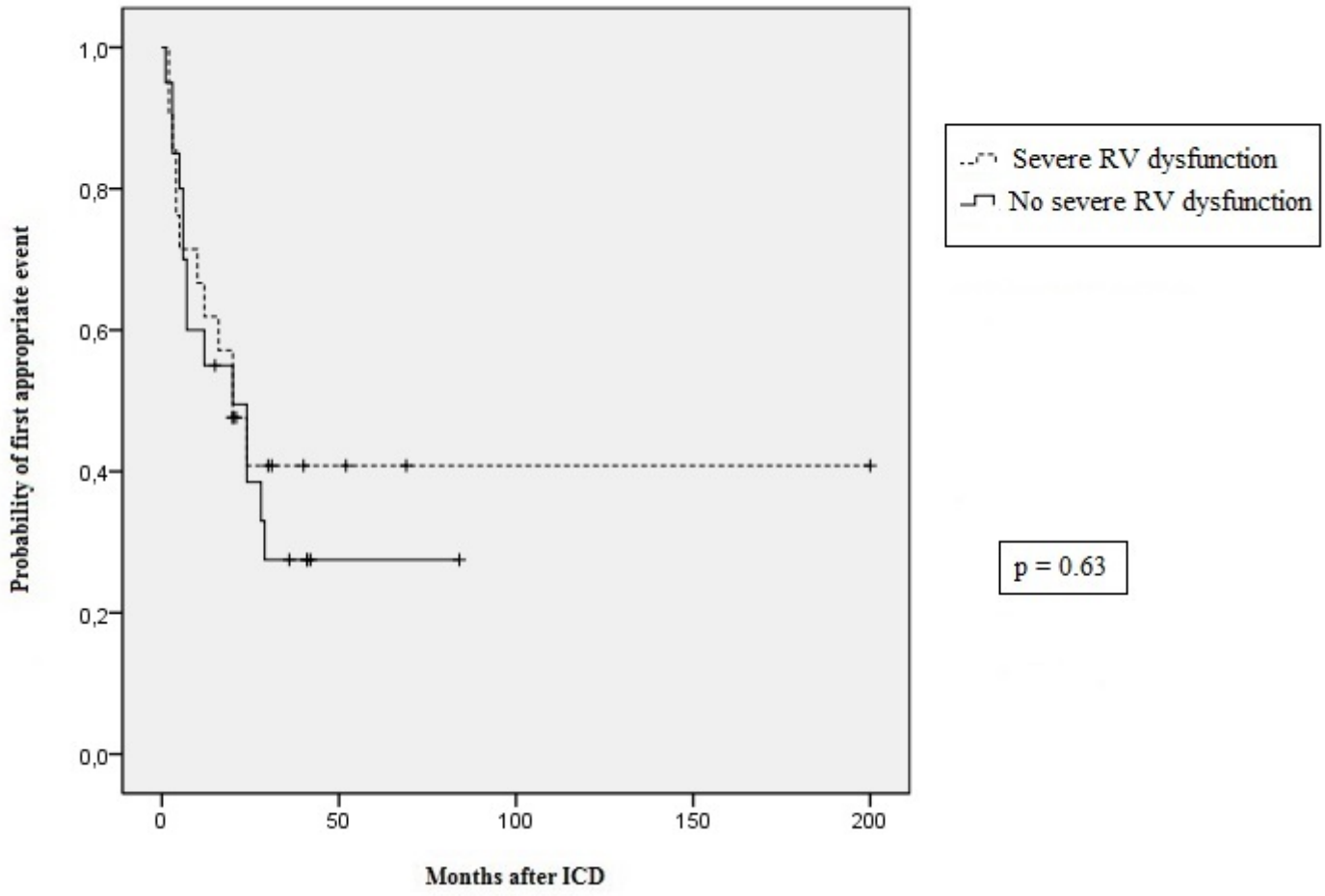

Figure 2

Kaplan-Meier graph showing the cumulative probability of the first appropriate arrhythmic event by the ICD according to the severe involvement of the RV (fractional area change ≤17% or RVEF≤35%) or not. ICD: implantable cardiac defibrillator.

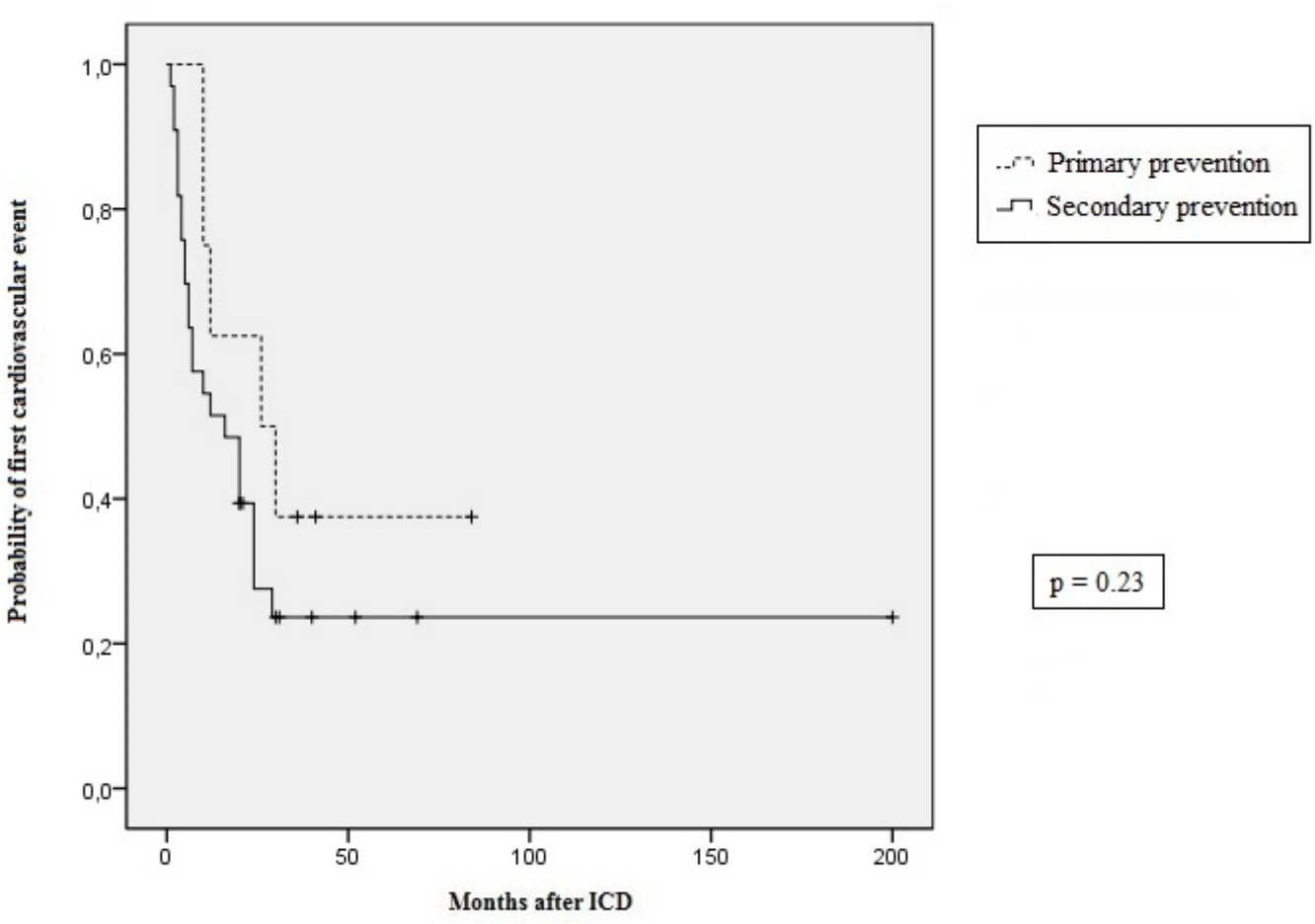

Figure 3

Kaplan-Meier graph showing the cumulative probability of the first cardiovascular event (ventricular arrhythmias, admission due to heart failure, heart transplantation or cardiovascular death) according to the indication of the ICD (primary and secondary prevention). ICD: implantable cardiac defibrillator.