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Letter to the Editor

Therapeutic management in Sicilian patients with definite arrhythmogenic right ventricular dysplasia/cardiomyopathy and focus on the role of implantable cardioverter-defibrillator therapy

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Arrhythmogenic Right Ventrticular Dysplasia/Cardiomyopathy (ARVD/C) is an inherited cardiomyopathy characterized by right ventricular myocyte loss with fibrofatty replacement, a high risk of ventricular arrhythmias (VA) and sudden cardiac death (SCD) [1]. Prevention of SCD represents the most important management strategy and the achievement of this target can be reached by different therapeutic strategies including implantable cardioverter-defibrillator (ICD) implantation, pharmacologic therapy, catheter ablation of ventricular tachycardia (VT) and cardiac transplantation [2,3]. The aim of this study is to examine the outcome of the different therapies adopted in a group of affected patients, focusing on the role and predictors of ICD therapy.

We conduced a multicenter study evaluating 28 patients (18 male; age 42 ± 14 years) with definite ARVD/C. Diagnosis of ARVD/C was based upon the 2010 revised Task Force Criteria [4] and only patients with definite diagnosis entered the study to enhance diagnostic specificity. Management therapy was established according to the clinical features and risk stratification of each patient. All patients were followed up at biannual and yearly intervals and data included invasive and noninvasive investigation, and device interrogation. The estimate of the potential survival benefit of ICD was limited to appropriate ICD shock therapies for episode of VF/VFL, since not any arrhythmic events necessarily correspond to the true arrhythmic risk of death. We studied our patients over a mean follow-up of 6.0 ± 4.4 years.

Antiarrhythmic drugs were used in 26 patients (93%), and in 13 patients (50%) this therapy was associated with ICD implantation [Sotalol in 11 patients (42%) such as amiodarone; β-blockers in 4 patient (15%)]. During the follow-up 8 patients (61%), that initially received only antiarrhythmic drugs, had an ICD implantation cause of the lack of arrhythmic control. Radiofrequency catheter ablation was performed in 6 patients (21%) and in no cases its efficacy was observed because of the recurrence of VT that required ICD implantation in whole cases. Cardiac transplantation was performed as a final therapeutic option due to refractory congestive heart failure in 3 patients (10%).

At the time of the diagnosis 15 patients (54%) received an ICD implantation based to the estimated risk of SCD, according with the last guidelines [5] for management of patients with VA. During the follow-up 8 patients (61%) received an ICD because of the relapse of arrhythmic events although they were using antiarrhythmic drugs or underwent catheter ablation. Twenty patients (86%) had received appropriate ICD therapy. An appropriate ICD shock intervention for ventricular fibrillation (VF)/ventricular flutter (VFL) was seen in 12 patients (52%). Compared with the 100% actual survival rate, VF/VFL-free survival rate was 96%, 94% and 51% respectively at 1, 5 and 10 years of follow-up (logrank $p < 0.0001$) (Fig. 1). The estimated mortality reduction at 1, 5, 10 years of follow-up was 4%, 6% and 49% and the average rate of ICD interventions for VF/VFL was 5%.

Univariate predictors of ICD shock therapy were a Holter premature ventricular complex (PVC) count >500/24 h (hazard ratio [HR]: 9.44; 95% confidence interval [CI]: 1.17 to 15.95; $p = 0.03$) and age presentation >44 years (HR: 3.71; 95% CI: 1.04 to 13.19; $p = 0.04$) (Table 1). Moreover, both of them remained as significant predictors on multivariable analysis. The positive predictive value (PPV) and the negative

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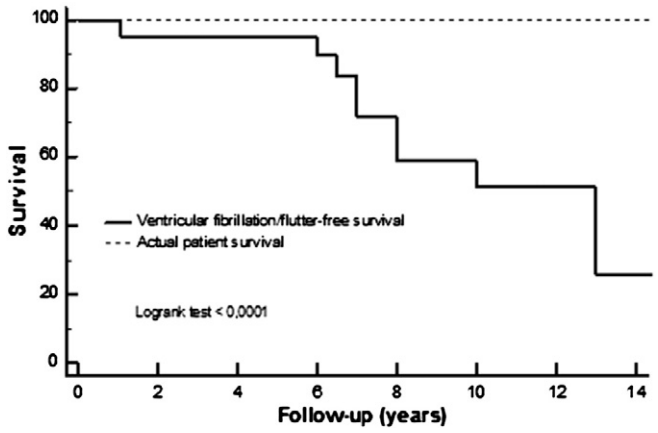

Fig. 1. Kaplan–Meier analysis of survival free of VF/VFL compared with actual patient survival. Divergence between lines reflects the estimated survival benefit of ICD therapy.

predictive value (NPV) of PVCs count >500/24 h were 88.9% and 77.7% respectively, sensitivity and specificity were 80% and 87.5% respectively. The cumulative survival rate free of ICD therapy at 10 years was higher (80%) in patients with low count of PVCs (≤500/24 h) compared with patients with a high count of PVCs (24.5%) (logrank $p < 0.01$). Also, the cumulative survival rate free of ICD therapy at 10 years was 71% in patients with age presentation ≤44 years compared with 37% in patients with age presentation >44 years (logrank $p = 0.02$). We finally analyzed the relationship between the number of risk factors and ICD shock therapy. We found that patients with one or two risk factors had a significantly increased risk of ICD therapy. The 5-year survival rates free of appropriate ICD shock therapy for patients with 0 or 2 risk factors were 100% and 75%, respectively (logrank $p = 0.002$).

The prevention of life-threatening arrhythmias is the most important management strategy in ARVD/C patients and risk stratification represents an essential step to achieve this target [6]. However in many cases the choice can be a difficult cause of the rarity and the clinical heterogeneity of the disease [7]. According to literature [8–10], even our study confirms the predominant role of ICD implantation as the first-line therapy and suggests the secondary employment of other therapeutic options, when used as unique treatment, only in patients with hemodynamically stable arrhythmias, or asymptomatic mutation carriers or patient with borderline or possible diagnosis of ARVD/C [6]. We moreover identified two clinical variables as significant predictors of appropriate ICD shock therapy and the combination of these risk factors portends an incremental risk. We thought that a very frequent Holter monitoring PVC count represents a marker of electrical instability leading to ventricular arrhythmias. Moreover patients whose presentation starts over the third decade, conceal an important anatomical damage, including myocardial and conduction tissue, underlying their high risk of VA. This finding can be usefully employed to risk-stratify patients who need ICD implantation.

Table 1
Predictors of appropriate ICD shock intervention.

Variable	Univariable analysis			Multivariable analysis		
	HR	95%CI	p value	HR	95%CI	p value
PVCs > 500/24 h on Holter monitoring	9.44	1.17–15.95	0.03	9.28	1.06–20.55	0.04
Age presentation > 44 years	3.71	1.04–13.19	0.04	6.07	1.02–2.5	0.04
NSVT	2.82	0.78–10.10	0.11	0.37	0.02–4.7	0.45
Syncope	0.64	0.19–2.11	0.47			
T wave inversion (V_1–V_3)	0.20	0.04–0.91	0.38			
Male gender	0.46	0.11–1.96	0.30			
Inducibility at EPS	1.80	0.34–9.29	0.48			
Epsilon wave	0.25	0.03–2.07	0.20			
Prolonged QRS duration	0.76	0.2–2.90	0.69			
Biventricular involvement	1.18	0.3–4.56	0.80			
Family history of sudden death	0.65	0.19–2.23	0.50			

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