# Treatment decision making in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy: State of the art

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Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is a genetic form of cardiomyopathy usually transmitted with an autosomal dominant trait, characterized by right ventricular myocyte loss with fibrofatty replacement [1]. Clinical presentations in patients with ARVD/C vary widely. Heart failure, ventricular arrhythmias (VA) and sudden cardiac death (SCD) are the most severe clinical manifestations of ARVD/C. It accounts for 11%–22% of cases of SCD in the young athlete population. Prevention of SCD represents the primary goal of management strategy in ARVD/C patients, and therapeutic options include antiarrhythmic drugs, the placement of an ICD, radiofrequency ablation and cardiac transplantation. In many cases the choice of a correct treatment is difficult due to the rarity of the disease, not allowing a standard treatment's managing. Therapeutic strategy has to be individualized, based on clinical presentation, risk stratification and physician preference [2,3]. Although several studies evaluated the benefit of the different therapeutic options, large prospective randomized trials are not available. Consequently, the current therapeutic recommendations for ARVD/C have been developed from observational studies [4] and case series. In order to improve therapeutic efficacy it is important to classify ARVD/C patients in 4 groups (Table 1): asymptomatic patients or healthy gene carriers, patients with hemodynamically stable arrhythmias (such as non-sustained or sustained VT), patients with cardiac arrest, syncope, or hemodynamically poorly-tolerated VT and patients with refractory congestive heart failure or untreatable ventricular arrhythmias. First group does not require prophylactic treatment. They should however undergo cardiac follow-up and exercise restriction especially when there is a family history of sudden death. Indeed excessive mechanical stress, such as during competitive sports activity and training, can aggravate the underlying myocardial lesion and accelerate disease progression [1]. In these patients moreover prophylactic therapy with β-blockers could further reduce the rate of ARVD/C progression. Pharmacologic treatments such as β-blockers and class-III antiarrhythmic agents (sotalol and amiodarone) are commonly used to reduce the burden of arrhythmias in patients with hemodynamically stable arrhythmias [4]. No clinical trial has studied the efficacy of antiarrhythmic drugs in the treatment of ventricular arrhythmias in patients with ARVD/C. Nevertheless, the evidence available has been derived from observational studies, which have shown conflicting results. The combination of beta-blockers and amiodarone has had a beneficial effect in suppression of non-sustained VT, reduction in the frequency of sustained ventricular arrhythmias, and reduction of VT rate preventing syncope and favoring antitachycardia pacing termination rather than shock therapy. Catheter ablation is another option for treatment of patients with ARVD/C who have recurrent ventricular arrhythmias despite treatment with antiarrhythmic drugs. Ablation is considered a complementary therapy to ICD useful to improve quality of life by decreasing the frequency of episodes of sustained VT, symptomatic NSVT, and ventricular ectopy. Nevertheless it may not be sufficient to prevent SCD because of the frequent relapses of VT [5]. However it is now well-established that the outcomes of VT ablation in patients with ARVD are improved with a combined endocardial/epicardial approach [4]. Philips B et al. recently revealed a very good short- and mid-term success rate with a cumulative freedom from VT after epicardial VT ablation of 64% and 45% at 1 and 5 years, respectively [6]. This could be explained by the preferential epicardial infiltration of the disease.

Indications of ICD for primary prevention of SCD in ARVC/D patients have not been well established [3,7]. At present ICD is recommended in all probands who meet TF criteria, especially if they have a history of sudden death, sustained VT, arrhythmogenic syncope, or a high degree of ventricular ectopy and/or nonsustained VT on Holter monitoring. Several studies of ARVD/C probands who received an ICD showed appropriate interventions during follow-up in more than 50% of patients and approximately 40% were considered life-saving based on the presence of rapid VT/VF [8,9]. We recently reported the results of a study that investigated the therapeutic management in a group of ARVD/C patients [10]. Twenty-three patients received an ICD, and over a mean follow-up of $6.0 \pm 4.4$ years, 20 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). These findings are important, as they demonstrate that more than half of the ARVD patients treated with an ICD experienced appropriate ICD interventions. Finally patients with late complications of the disease, developing heart failure or life threatening and untreatable VT, heart transplantation could be an option with good short and long term survival. This approach is essentially the final therapeutic option for these patients [1]. ARVC/D is a progressive disease with different genotypic and phenotypic variations that often do not allow a standard treatment's managing. The main goal is to improve the risk stratification for better identification of high risk patients, who need the best management, from restriction of physical activity, antiarrhythmic drugs, ICD placement, new ablation approaches with simultaneous endocardial and epicardial ablation and, if necessary, heart transplantation. These interventions are often life saving, with the potential to change the natural history of the disease by offering a good quality and better life expectancy.

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**Table 1**
Recommendations for clinical management in patients with ARVD.

| Subgroups | Recommendations |
|---|---|
| Asymptomatic patients or healthy gene carriers | – Physical exercise restriction;<br>– Pharmacologic therapy (β-blockers and class-III antiarrhythmic agents). |
| Patients with hemodynamically stable arrhythmias | – Pharmacologic therapy (β-blockers and class-III antiarrhythmic agents);<br>– Radiofrequency catheter ablation for the treatment of VA. |
| Patients with cardiac arrest, syncope, or hemodynamically poorly-tolerated VT | – ICD implantation. |
| Patients with refractory congestive heart failure or untreatable ventricular arrhythmias | – Heart transplantation. |

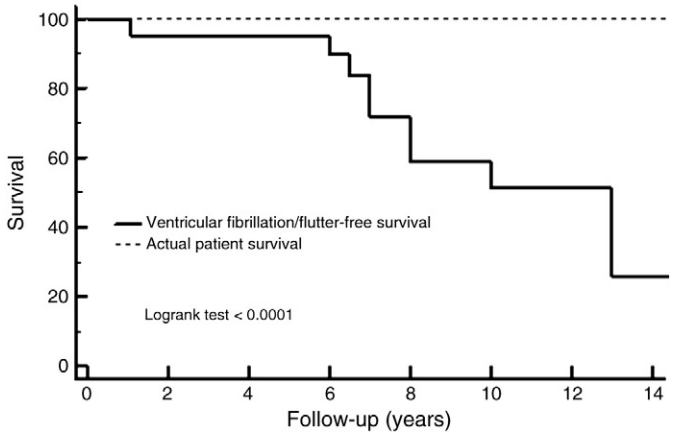


**Fig. 1.** Kaplan–Meier analysis of survival free of VF/VFL compared with actual patient survival. Divergence between lines reflects the estimated survival benefit of ICD therapy.

## References

[1] Calkins H. Arrhythmogenic right ventricular dysplasia. Curr Probl Cardiol 2013 Mar;38(3):103–23.
[2] Smith W. Guidelines for the diagnosis and management of arrhythmogenic right ventricular cardiomyopathy. Heart Lung Circ 2011;20(12):757–60.
[3] Zipes DP, Camm AJ, Borggrefe M, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (writing committee to develop guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Circulation 2006;114:e385–484.
[4] Fernández-Armenta J, Brugada J. Arrhythmogenic right ventricular dysplasia. 10ESC Council for Cardiology Practice, N°26; 2012.
[5] Dalal D, Jain R, Tandri H, et al. Long-term efficacy of catheter ablation of ventricular tachycardia in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy. J Am Coll Cardiol 2007;50:432–40.
[6] Philips B, Madhavan S, James C, et al. Outcomes of catheter ablation of ventricular tachycardia in arrhythmogenic right ventricular dysplasia/cardiomyopathy. Circ Arrhythm Electrophysiol 2012;5:499–505.
[7] Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 Guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (writing committee to revise the ACC/AHA/NASPE 2002 Guideline update for implantation of cardiac pacemakers and antiarrhythmia devices): developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. Circulation 2008;117(21):e350–408.
[8] Bhonsale A, James CA, Tichnell C, et al. Incidence and predictors of implantable cardioverter defibrillator therapy in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy undergoing implantable defibrillator implantation for primary prevention. JACC 2011;58:1485–96.
[9] Corrado D, Leoni L, Link MS, et al. Implantable cardioverter-defibrillator therapy for prevention of sudden death in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia. Circulation 2003;108(25):3084–91.
[10] Inciardi RM, Rotolo A, Coppola G, et al. Therapeutic management in Sicilian patients with definite arrhythmogenic right ventricular dysplasia/cardiomyopathy and focus on the role of implantable cardioverter-defibrillator therapy. Int J Cardiol 2014 Apr 1;172(3):468–9.

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