



Antiarrhythmic Treatment of Arrhythmogenic Right Ventricular Cardiomyopathy: Drugs, Catheter Ablation, or ICD?

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Abstract

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a major cause of sudden cardiac death and ventricular tachyarrhythmias in young, apparently healthy individuals and athletes. Myocardial atrophy with subsequent fibrofatty replacement predominantly affects right ventricular myocardium and results in global and regional dysfunction as well as areas of slow conduction and dispersion of refractoriness which are prerequisites for reentrant ventricular tachyarrhythmias.

Patients affected with ARVC should be excluded from competitive sports and vigorous training. To provide optimal treatment, a detailed diagnostic evaluation and risk stratification is mandatory. Tailored treatment strategies aim at the suppression or effective termination of recurrent ventricular tachyarrhythmias and prevention of sudden death by antiarrhythmic drug therapy, catheter ablation, or implantation of a cardioverter-defibrillator (ICD).

Antiarrhythmic drugs may be used as a stand-alone treatment to suppress VT recurrences in patients with ARVC and low risk of sudden death. Sotalol (preferred) or amiodarone in combination with β -blockers showed the highest efficacy rates. In patients at higher risk, an ICD should be implanted and antiarrhythmic drugs be used only as an adjunct to prevent or suppress frequent VT recurrences and ICD discharges.

Catheter ablation using conventional or electroanatomic mapping techniques yields good acute results for eliminating the targeted arrhythmia substrate. However, during the progressive long-term course of ARVC, VT recurrences from new arrhythmia foci are frequent and therefore limit the curative value of catheter ablation. In patients with frequent VT recurrences and ICD discharges however, catheter ablation plays an important role as a palliative and adjunctive treatment option for arrhythmia suppression.

ICD implantation has been increasingly used for secondary and also primary prevention of sudden death in patients with ARVC. In secondary prevention, the ICD has shown to improve the long-term prognosis of patients at high risk of sudden death by effective termination of life-threatening recurrences of ventricular tachyarrhythmias. However, adequate lead placement may be difficult and lead-related complications during long-term follow-up must be taken into account. The role of ICD therapy for primary prevention of sudden death in ARVC is not yet adequately defined.

Ongoing international registries will provide important additional data to improve risk stratification and refine treatment algorithms in order to select the best individual treatment for arrhythmia suppression and prevention of sudden death in patients with ARVC.



Introduction

Arrhythmogenic right ventricular cardiomyopathy / dysplasia (ARVC) is a major cause of ventricular tachyarrhythmias and sudden death in young patients and athletes with apparently normal hearts. The disease is characterized by localized or diffuse atrophy of predominantly right ventricular myocardium with subsequent replacement by fatty and fibrous tissue (1-4). These structural abnormalities are mainly located in the outflow tract, apex and subtricuspid area of the right ventricular free wall („triangle of dysplasia“) (4). The interventricular septum and the left ventricular myocardium are usually spared in early disease stages but may be involved during more advanced manifestations of ARVC. As a result of these pathomorphological alterations, global and regional right (and left) ventricular dysfunction and ventricular tachyarrhythmias due to areas of slow conduction and dispersion of refractoriness are the major clinical findings and manifestations of ARVC.

Clinical and molecular genetics recently identified mutations in genes encoding for desmosomal cell adhesion proteins such as plakoglobin, plakophilin-2 and desmoplakin as well as the transforming growth factor- β 3, which modulates the expression of cell-contact proteins (5-8). These genetic mutations result in haploinsufficiency and reduced expression of desmosomal proteins, which may predispose mechanical cell contacts to rupture, potentially triggered by stretch of the right ventricular free wall during exercise or sports activity. This pathophysiological concept would explain the high prevalence of ARVC among athletes, the dominant manifestation in the right ventricle and the frequent provocation of arrhythmias during exercise in ARVC (9-10).

Clinical presentation

ARVC usually presents with ventricular tachyarrhythmias of left bundle branch block configuration in apparently healthy adolescents or young adults. In the majority of cases, the age at the time of first manifestation ranges between 15 and 35 years. In contrast, first symptoms of ARVC during early childhood or beyond the age of 60 years are unusual. Men are more frequently affected than women and usually present with more extensive disease expression (4, 11)

In the majority of patients, ARVC manifests with the sporadic occurrence of monomorphic ventricular tachycardia (VT). Others present with frequent premature ventricular beats, repetitive ventricular runs, or nonsustained VT. Associated symptoms span from palpitations and paroxysmal tachycardia to dizziness, syncope and sudden cardiac arrest. Diagnostic criteria were proposed by an international study group (12) (table 1), but have not yet been prospectively validated.



Table 1: Diagnostic Criteria of ARVC. Two major criteria, one major and two minor criteria, or 4 minor criteria from different categories qualify for the diagnosis of ARVC (adapted from 12). *EF: ejection fraction; LBBB: left bundle branch block; LV= left ventricle; RBBB: right bundle branch block; RV: right ventricle; VT: ventricular tachycardia*

I. Global and/or regional RV dysfunction and structural RV alterations *	
major	<ul style="list-style-type: none"> – severe dilatation and reduction of RV-EF with no (or only mild) LV involvement – localized RV aneurysms (akinesia or dyskinesia with diastolic bulging) – severe regional dilatation of RV
minor	<ul style="list-style-type: none"> – mild global RV dilatation and/or reduced RV-EF with normal LV – mild segmental RV dilatation – regional RV hypokinesia
II. Tissue characterization of ventricular walls	
major	<ul style="list-style-type: none"> – fibrofatty replacement of myocardium in endomyocardial biopsy
III. Repolarisation abnormalities	
minor	<ul style="list-style-type: none"> – Inverted T-waves in right precordial ECG leads (V_2 and V_3) (age >12 years, no RBBB)
IV. Depolarisation / Conduction abnormalities	
major	<ul style="list-style-type: none"> – Epsilon-Potentials or QRS prolongation (>110 ms) in right precordial leads (V_1-V_3)
minor	<ul style="list-style-type: none"> – Late potentials (signal-averaged ECG)
V. Arrhythmias	
Minor	<ul style="list-style-type: none"> – LBBB type VT (sustained or nonsustained (ECG, Holter, exercise testing) – frequent ventricular extrasystoles (>1000 / 24 hrs on Holter)
VI. Family history	
major	<ul style="list-style-type: none"> – familial disease confirmed at necropsy or surgery
minor	<ul style="list-style-type: none"> – family history of premature sudden death (<35 years) due to suspected ARVC – family history of ARVC (clinical diagnosis based on present criteria)

* detected by echocardiography, angiography, magnetic resonance imaging, or radionuclide ventriculography

Patients with ARVC are usually not limited in exercise capacity and frequently participate in sports or even athletic competitions. Particularly in early stages of ARVC, ventricular arrhythmias and cardiac arrest frequently occur during or immediately after physical exercise and may be triggered by catecholamines. Autonomic dysfunction with abnormal adrenergic stimulation of the myocardium and subsequent reduction of β -adrenoceptor density was demonstrated by quantitative positron emission tomography and provided a pathophysiological rationale for these clinical observations (13). With increasing age and more advanced stages of ARVC, the exercise-dependence of VT diminishes and the arrhythmias more frequently occur also at rest.



In recent years, ARVC is of increasing interest in sports medicine, particularly with regard to sports eligibility, pre-participation screening and follow-up evaluation of athletes. Because of the increased risk of sudden death due to ventricular arrhythmias (14) and the potential for accelerated disease progression due to the genetically determined damage of mechanical cell contacts, patients with ARVC should be advised against strenuous exercise and vigorous training and should be excluded from participation in competitive or professional athletic sports (10).

Treatment of heart failure

Symptomatic heart failure requiring treatment is present in only 10% to 20% of patients with ARVC. It is unusual as an early manifestation of ARVC and almost exclusively occurs in patients with a long history and advanced stages of the disease. In addition to progressive dilatation and global dysfunction of the right ventricle, these patients frequently demonstrate left ventricular involvement and therefore exhibit clinical symptoms of biventricular heart failure (15).

In the lack of causal treatment options for heart failure in ARVC, pharmacological therapy follows conventional guidelines including vasodilators, diuretics, β -blockers, and digitalis. In the rare situation of severe and intractable progressive heart failure, cardiac transplantation has been successfully performed by our group and others.

Treatment of arrhythmias

The prognosis of ARVC is mainly determined by ventricular tachyarrhythmias and sudden cardiac death. In a young population of sudden death victims below the age of 35 years, the proportion of ARVC as the underlying disease has been estimated with 10% to 25% (14, 16). This corresponds with a 20% to 25% mortality rate after 10 years on empiric (uncontrolled) antiarrhythmic drug therapy (17-20). Therefore, ARVC is not a benign disease but requires an individualized, tailored and effective treatment to reduce symptoms and to prevent sudden cardiac death. Therapeutic options include antiarrhythmic drug therapy, catheter ablation and the implantation of a cardioverter-defibrillator (ICD).

Antiarrhythmic Drug Therapy

In patients with ARVC and no history of syncope or cardiac arrest, premature ventricular beats, couplets or short ventricular runs are usually not associated with an increased arrhythmic risk and therefore do not require specific antiarrhythmic treatment. In many cases, reassurance of the patient results in an improvement of symptoms. However, should a patient still suffer severe symptoms from palpitations, treatment with conventional β -blockers

or verapamil may be considered. β -blockers appear to more effective in patients with exercise-provocable ventricular arrhythmias, whereas verapamil may be more successful in arrhythmias which occur at rest and are suppressed during exercise. Specific antiarrhythmic drugs or catheter ablation should be limited to patients with significant symptoms refractory to these measures.

In patients with ARVC and sustained VT, antiarrhythmic drug therapy aims at the suppression of VT recurrences, the reduction of emergency hospital admissions, and (most importantly) the prevention of sudden cardiac death. Prospective and randomized studies on antiarrhythmic drug efficacy in ARVC are not available.

The largest experience on the acute and long-term efficacy of antiarrhythmic drug therapy in ARVC was published by Wichter et al. (21) and includes 191 patients with 608 drug tests in their latest published series (22) (Figure 1).

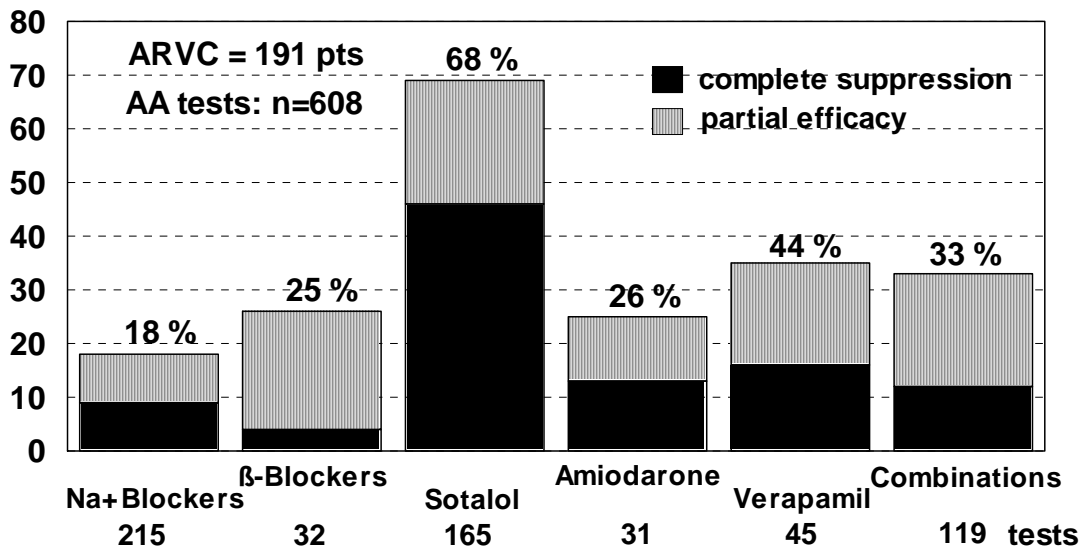


Figure 1. Efficacy rates of different antiarrhythmic drugs for treatment of VT in ARVC (n=191 patients, n=608 tests). Sotalol in a dosage of 320-480 mg/day showed the highest efficacy rates. Amiodarone mono-treatment was less effective than sotalol and therefore appears to be no alternative of first choice. Verapamil was tested only in patients with nonreentrant VT and may only be an alternative in VT underlying triggered activity or abnormal automaticity (see text for details; adapted from 22).

Sotalol in a dosage of 320 mg to 480 mg/day (up to 640 mg/day in selected cases) was identified as the most effective drug, resulting in a 68% overall efficacy rate. A combination of amiodarone with β -blockers has a similar antiarrhythmic profile (class-III activity plus β -blockade) and was reported with comparable efficacy rates by French authors (23). However, given the high incidence of serious side effects during long-term treatment with amiodarone in a young patient cohort, sotalol or nonpharmacological treatment options were preferentially used in our patients.



Class-I antiarrhythmic drugs proved efficacious in only a minority of patients with ARVC (18%), although some patients received several different class-I drugs to suppress the clinical arrhythmia (21-22). Similar results were reported by other groups (23-24). In a small subset of patients with ARVC and triggered activity or abnormal automaticity as underlying arrhythmia mechanisms, verapamil and β -blockers demonstrated efficacy rates of 44% and 25% (22). However, to suppress the clinically dominant reentrant ventricular arrhythmias in ARVC, verapamil and β -blockers are usually not effective.

Overall, serial testing identified an antiarrhythmic drug, which completely suppressed the clinical arrhythmia in 118 of 191 patients (62%). Another 13% of patients were discharged on partially effective antiarrhythmic drugs, based on clinically sufficient arrhythmia suppression or more difficult inducibility of VT during serial electrophysiologic study (22). Multivariate analysis identified extensive right ventricular dysfunction and the inducibility of VT during programmed electrical stimulation as independent predictors of drug refractoriness.

Adequate monitoring of drug efficacy is a prerequisite for antiarrhythmic drug therapy in ARVC. Serial electrophysiologic study (inducible VT) or Holter monitoring combined with exercise testing (noninducible VT) provided better long-term outcome when compared with empiric drug treatment. The arrhythmia recurrence rate was low in patients who were discharged on a drug tested effective, whereas sudden deaths and VT recurrences predominantly occurred in patients with insufficient suppression of arrhythmias at discharge, those with significant progression of ARVC, or those with inappropriate dosage (noncompliance) of the tested antiarrhythmic drug (22) (figure 2).

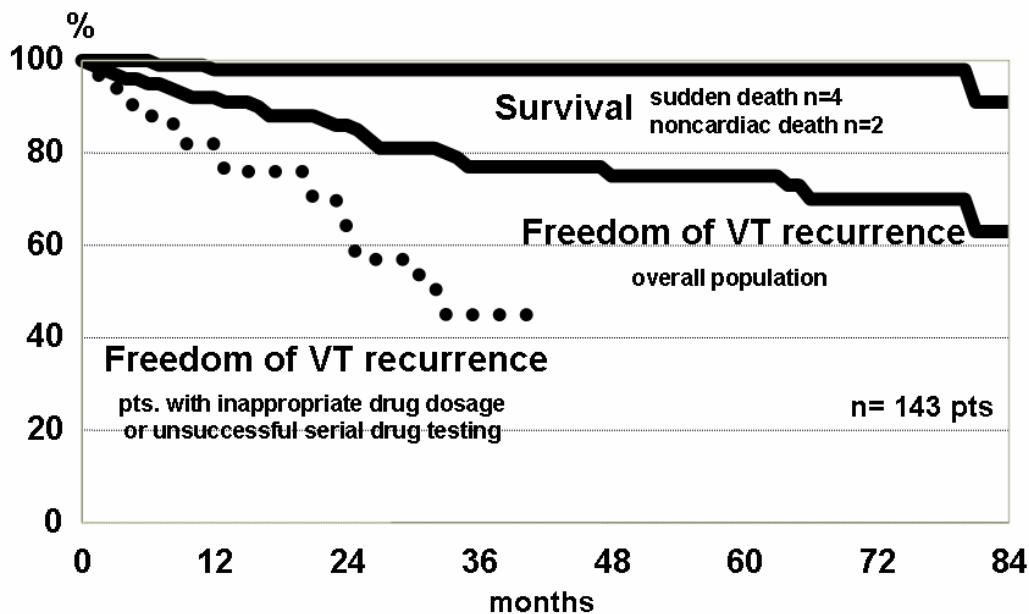


Figure 2. Long-term outcome of 143 patients with ARVC and low risk of sudden death discharged on antiarrhythmic drugs after serial drug testing (follow-up: 53±32 months). The incidence of sudden death was low, the recurrence rate of VT was acceptable (25% after 5 years). In the subgroup of patients with inappropriate drug dosage (noncompliance) or unsuccessful serial drug testing, the VT recurrence rate approached 60% after 3 years (22).

Catheter Ablation

In patients with ARVC, the arrhythmogenic substrate is represented by progressive atrophy predominantly of right ventricular myocardium with subsequent replacement by fatty and fibrous tissue (1-4). The presence of surviving myocytes interspersed within fat and fibrosis results in areas of slow conduction and dispersion of refractoriness, predisposing to reentrant arrhythmias. The anatomic substrate is comparable to that in patients with VT after myocardial infarction, in which viable myocardial fibers survive within fibrotic scar tissue at the border zone of the infarcted area.

Endocardial catheter mapping using pacing interventions demonstrated that reentrant mechanisms underly VT in the majority of ARVC patients. Our group (25) and others (26-28) showed that conventional mapping criteria developed for catheter ablation of VT in patients after myocardial infarction can also be applied in patients with ARVC. In particular, activation mapping, middiastolic potentials and entrainment mapping are useful techniques to confirm the presence of areas of slow conduction and to localize the critical sites for energy delivery. In patients with localized or concealed forms of ARVC and mechanisms of triggered activity and abnormal automaticity, pace mapping may be helpful to identify the target area for energy delivery during catheter ablation.

More recently, three-dimensional mapping techniques such as electroanatomical (CARTO[®]) (29-31) and non-contact (EnSite[®]) (32) mapping were used to identify the target regions for linear ablation lesions to facilitate substrate modification, even under conditions of hemodynamically unstable VT unsuitable for conventional mapping of VT. Although these new mapping technologies simplify the mapping procedure and thereby shorten intervention and fluoroscopy times, they have not yet demonstrated an improvement of acute efficacy and long-term outcome of catheter ablation in ARVC.

In the early reports, catheter ablation was performed using direct current (DC) energy which was later replaced by radiofrequency current (RF) which is still the technique most widely used today. The published results of catheter ablation in ARVC demonstrate that acute success can be achieved in 60-80% of patients. However, during long-term follow-up of 3-5 years, the recurrence rates were reported as high as 50-70%.

Fontaine et al. (26) studied the acute results and follow-up of DC and/or RF catheter ablation of VT in 50 patients with ARVC and reported an overall clinical success rate of 81% for DC ablation (fulguration) and 93% of combined DC and RF ablation. The clinical VT was suppressed completely in 52% with DC and 79% with DC+RF ablation. To achieve these results, a second (n=35) or third (n=14) ablation session was necessary in 64% of patients. The incidence of recurrent VT during long-term follow-up was not reported in this study.

Ellison et al. (28) published their results of entrainment mapping and RF catheter ablation of 19 VTs in 5 patients with ARVC. VT terminated at 13 sites or 22% of RF applications. Eight of the 19 VTs were rendered noninducible and another 3 were modified. No procedure-related complications were observed. However, only one patient with VT originating from the right ventricular outflow tract has remained free of VT during post-procedural EP testing and follow-up.

Wichter et al. (25) reported their experience with catheter ablation in 30 patients with ARVC. Favorable acute results with complete suppression of drug-refractory VT were achieved in 22 patients (73%). However, the long-term results were less satisfactory with two sudden cardiac arrests (6,7%) and 18 patients (60%) suffering from VT recurrence (n=16) or syncope (n=2) during a follow-up period of 52±37 months. Event-free survival was 63% after 1, 43% after 3 and 32% after 5 years, respectively (Figure 3) (25). The majority of early VT relapses (≤1 year) was due to the clinical arrhythmia and preferentially occurred in patients with primarily unsuccessful ablation. In contrast, the majority of late VT recurrences (>1 year) showed a different QRS morphology when compared with the target VT.

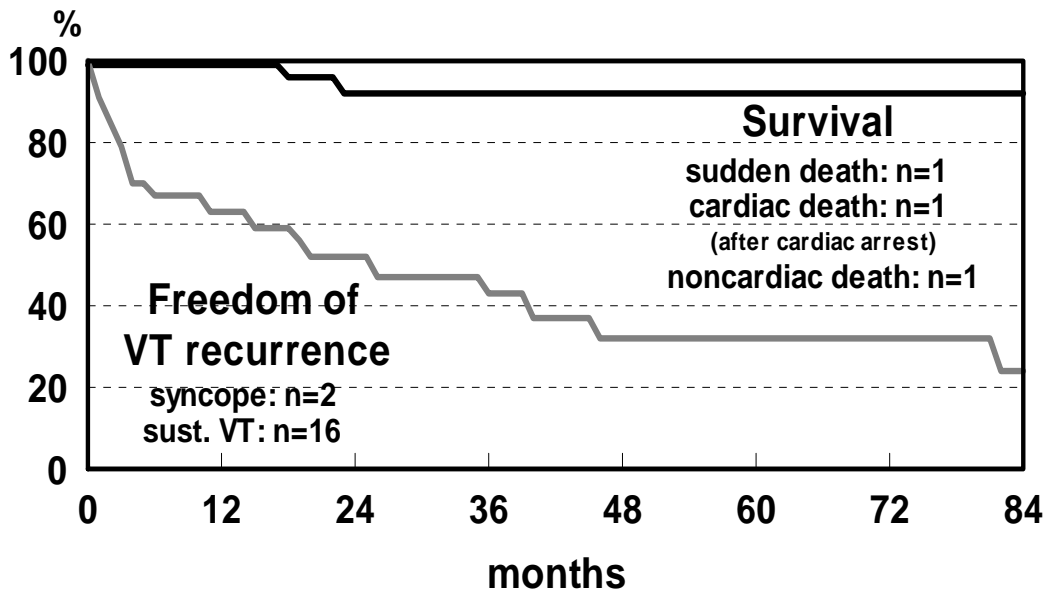


Figure 3. Long-term results after catheter ablation of VT in 30 patients with ARVC (follow-up: 52±37 months). Despite a rate of 73% acute success, the event-free survival was as low as 63% after one, 43% after three and 32% after five years. The majority of late VT recurrences (>1 year) was due to new VT morphologies (new arrhythmogenic foci) during the progressive long-term course of ARVC (adapted from 25).

Shoda et al. (33) reported similar results and achieved acute success in 10 of 11 ARVC patients (91%) using DC catheter ablation. However, 5 of them (50%) suffered VT relapses during follow-up of 15±4 months with QRS morphologies different from the ablated VT.

These observations suggest that new arrhythmogenic substrates may develop during the progressive long-term course of ARVC that may be responsible for VT recurrences and sudden cardiac death occurring late after initially successful catheter ablation of the targeted arrhythmia. This hypothesis also explains the discrepancy between the favorable acute results and the unsatisfactory long-term efficacy of catheter ablation for the treatment of VT in ARVC.

Therefore, although successful catheter ablation of VT offers the potential for long-term cure of the targeted and ablated VT, this treatment option has limited long-term efficacy in patients with ARVC. Current indications include those patients with localized forms of the disease and only a single morphology of well tolerated VT (curative approach) and those with frequent recurrences of drug-refractory or incessant VT or frequent ICD discharges (palliative approach). In the latter patients, catheter ablation may be the favored or even only available treatment option. However, it frequently requires additional antiarrhythmic drug therapy or repeated ablation sessions to

provide clinical success and should be combined with ICD-implantation to prevent sudden cardiac death during the progressive long-term course of ARVC.

Implantable Cardioverter-Defibrillator (ICD)

The implantation on a cardioverter-defibrillator (ICD) is increasingly used for secondary and also primary prevention of sudden death in patients with ARVC. However, no prospective randomized trials have compared ICD-implantation with antiarrhythmic drugs or catheter ablation in patients with ARVC.

The available information of ICD-therapy in ARVC is summarized in Table 2 and indicates that the majority of patients receive appropriate ICD therapies within the first year after ICD implantation. These ICD therapies were probably life-saving in a relevant proportion of patients because of the high rate of VT recurrences. Therefore, it is assumed that ICD-therapy improves the long-term prognosis and survival of patients with ARVC when applied to a selected high-risk population with otherwise normal life expectancy.

Table 2. Studies on ICD-Therapy in ARVC

Author	Year	Pts (n)	Study type	Men	Follow-up (months)	Primary Prevention	Mortality overall	Appropriate ICD-Therapy	Life-Saving ICD-Therapy	Complications
Breithardt (34)	1994	18	SC	72%	17±11	0%	0%	50%	NR	NR
Link (35)	1997	12	SC	58%	22±13	0%	8%	67%	50%	33%
Tavernier (36)	2001	9	SC	89%	32±24	0%	0%	78%	44%	NR
Corrado (38)	2003	132	MC	70%	39±25	22%	3%	48%	24%	14%
Wichter (37)	2004	60	SC	82%	80±43	7%	13%	68%	40%	45%
Rougin (39)	2004	42	MC	52%	42±26	40%	2%	78%	NR	14%
Hodgkinson (40)	2005	48	MC	63%	31	73%	0%	70%*	30%*	6%

* 5-year cumulative frequency for first appropriate ICD discharge

MC: multicenter study; NR: not reported; Pts: patients; SC: single-center study.

After previous reports from our group (34) and others (35-36) in small cohorts, we recently published the largest single-center experience of ICD-therapy in ARVC available to date (37). It comprises a considerable number of 60 well characterized consecutive high-risk ARVC patients and provides almost complete information on the very long-term follow-up (80±43 months) on recurrent ventricular tachyarrhythmias and complications after ICD implantation. In this cohort, ICD implantation was mainly indicated for secondary prevention after resuscitated

cardiac arrest or sustained VT. The results highlight the beneficial role of ICD-therapy in ARVC with respect to arrhythmic events and survival. Recurrent ventricular tachyarrhythmias were treated by either cardioversion (n=31) and/or antitachycardia pacing only (n=10) in 41 of 60 patients (68%). Most episodes were terminated by overdrive pacing. Event-free survival rates were 49%, 30% and 26% after one, three and five years, respectively. The projected benefit on survival by ICD therapy, calculated by the difference between total mortality and the incidence of fast VT (>240 bpm), was 21%, 32%, and 36% after one, three, and five years, respectively (37) (table 3, figure 4). These calculations assume that VT recurrences >240 bpm would have been fatal without ICD intervention, but also that all VT relapses ≤240 bpm would have been survived. The data therefore strongly suggest the beneficial role of ICD therapy in selected high-risk subgroups of ARVC.

	1 year (55 pts)	3 years (49 pts)	5 years (40 pts)	7 years (29 pts)	10 years (13 pts)
All-cause mortality	100	94	94	87	76
Estimated ICD benefit	21	32	36	35	28
Fast VT/VF	79	64	59	56	52
Any VT/VF	49	30	26	26	26
VT Cluster	83	73	69	69	65
Any AE	90	78	56	42	37
Severe AE	90	82	64	56	50
Lead-related AE	95	85	74	63	53
Undersensing	96	95	92	89	86

Table 3. Long-term follow-up results after implantation of a cardioverter-defibrillator (ICD) in 60 patients with arrhythmogenic right ventricular cardiomyopathy (ARVC). Results are given as percentage for the estimated benefit of ICD therapy on survival of life-threatening ventricular tachycardia/fibrillation (VT/VF) or freedom of events (see text for details) (37). AE: adverse event.

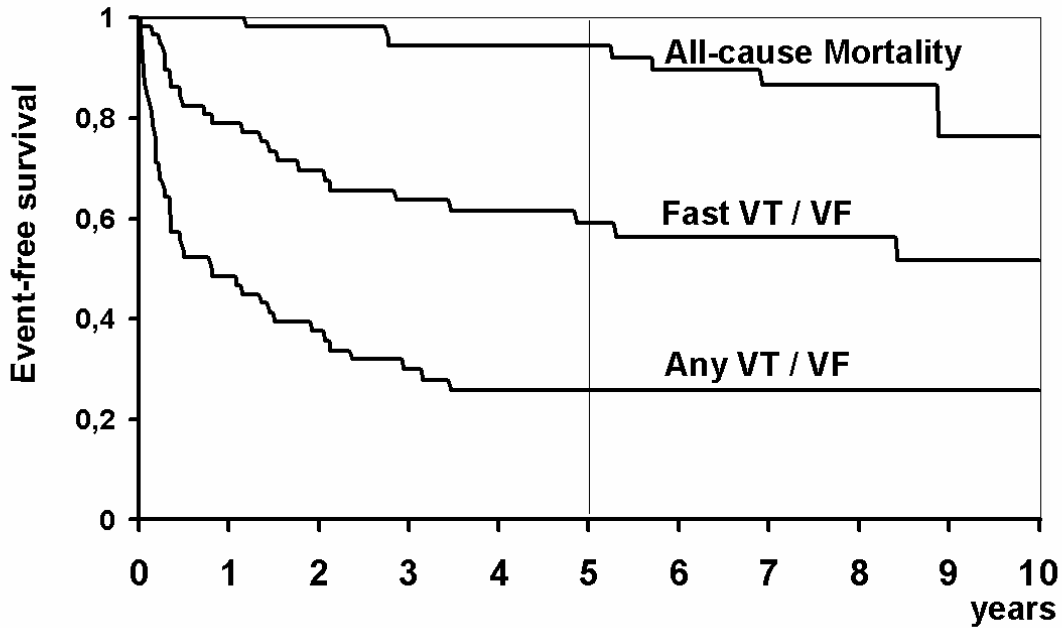


Figure 4. All-cause mortality and recurrence of ventricular tachycardia or fibrillation (VT/VF) during follow-up (80 ± 43 months) after ICD implantation in 60 patients with ARVC and high risk for sudden death. Kaplan-Meier curves depict freedom of all-cause mortality, fast VT/VF (>240 bpm) and VT/VF at any rate. The estimated benefit on survival from the ICD is calculated as the difference between all-cause mortality and fast VT/VF (adapted from 37)

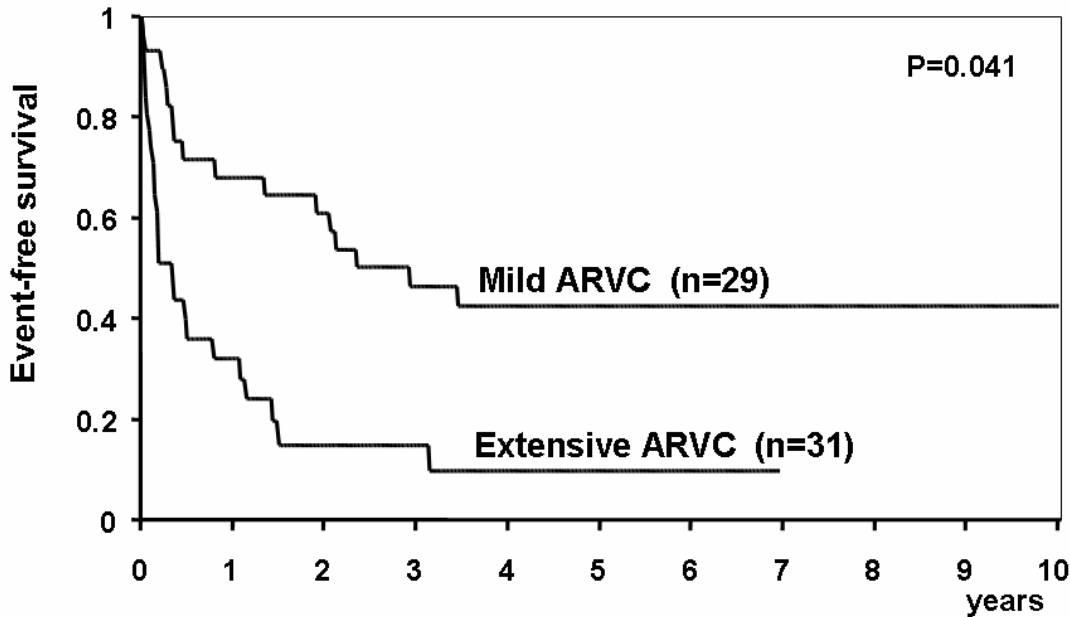


Figure 5. Multivariate Cox regression analysis identified extensive RV dysfunction as an independent predictor ($p=0.041$) of appropriate ICD therapies for VT/VF during long-term follow-up (80 ± 43 months) in ARVC (adapted from 37)

Multivariate analysis identified extensive RV dysfunction (OR 2.09; CI 1.03-4.24; $P=0.041$) as an independent predictor of appropriate ICD therapy during follow-up (figure 5). Inducible VT/VF during electrophysiologic study (OR 2.16, CI 0.94-5.0, $P=0.069$) and LV involvement (OR 1.94, CI 0.93-4.05, $P=0.078$) showed a trend toward statistical significance in the multivariate model. Inducible VF during electrophysiologic study was the only clinical variable during univariate Cox regression analysis that was associated with fast VT/VF recurrences during follow-up (37).

Corrado et al. (38) recently reported similar results of ICD therapy in a multicenter study of 132 ARVC patients. During follow-up of 39 ± 25 months, 48% of patients received appropriate ICD interventions, which were potentially life-saving in 24% of patients. A history of cardiac arrest or ventricular tachycardia with hemodynamic compromise, younger age, and left ventricular involvement were independent predictors of potentially lethal ventricular arrhythmias, whereas electrophysiological study results were of limited value to identify patients at risk.

Rougin et al. (39) published the North American multicenter experience of ICD implantation in 42 ARVC patients. Almost half of these patients received the device prophylactically for primary prevention of sudden death due to familial ARVC or sudden death, or minor symptoms which led to the diagnosis of ARVC. During follow-up of 42 ± 26 months, there was no difference between secondary and primary prevention indication with regard to appropriate ICD therapies. Multivariate analysis identified the inducibility of VT during programmed stimulation as an independent predictor of ICD firing.



Recently, Hodgkinson et al. (40) investigated the role of ICDs in an autosomal form of familial ARVC where a 3p25 DNA haplotype (ARVD-5) segregates with disease. A unique and first-time feature of that study is the comparison of an ICD-treated group of patients with a matched historical control group of similar risk profile within a genetically homogeneous ARVD-5 population. In a subgroup of 58 high-risk subjects, male patients were at a significantly higher risk of death when compared with females (odds ratio: 5.1). In the same 5-year period, ICD therapies for any VT occurred in 70% and for VT >240 bpm (potentially life-threatening) in 30% of patients, thus well comparable with previous studies. Similarly, the reported 28% 5-year total mortality reduction in male patients with an ICD correlates excellent with the estimated benefit of ICD-therapy on survival reported in previous publications. Furthermore, the time to first ICD discharge for VT >240 bpm was similar to the time of death in the control group. These data therefore confirm our concept of “hypothetical death” in ARVC, which calculates the benefit of ICD-therapy on survival by the difference between total mortality and the occurrence of potentially lethal VT >240 bpm, terminated by the ICD (37). Interestingly, the incidence of VT recurrences in Hodgkinson’s study (40) was irrespective of the indication for ICD implantation (primary or secondary prevention). This supports the potential benefit of ICD implantation for primary prevention of sudden death in high-risk cohort of genetically selected patients with ARVC. In the general ARVC population, however, the criteria for optimal selection of patients who benefit from ICD implantation for primary prevention remain to be defined (41).

In the published series of ICD implantation in ARVC, there is a low risk of procedure-related complications. In particular, there were no perioperative deaths or right ventricular perforations. However, due to the structural abnormalities of the right ventricular myocardium in patients with ARVC, meticulous attention has to be paid to the placement of the right ventricular defibrillation lead during lead implantation, in order to achieve satisfactory acute and long-term pacing and sensing results (37)

Progression of myocardial atrophy and subsequent replacement by fat and fibrosis at the site of lead implantation may result in a loss of sensing function of the right ventricular defibrillation lead and may require lead revision or the implantation of an additional pace/sense lead (Figure 6).

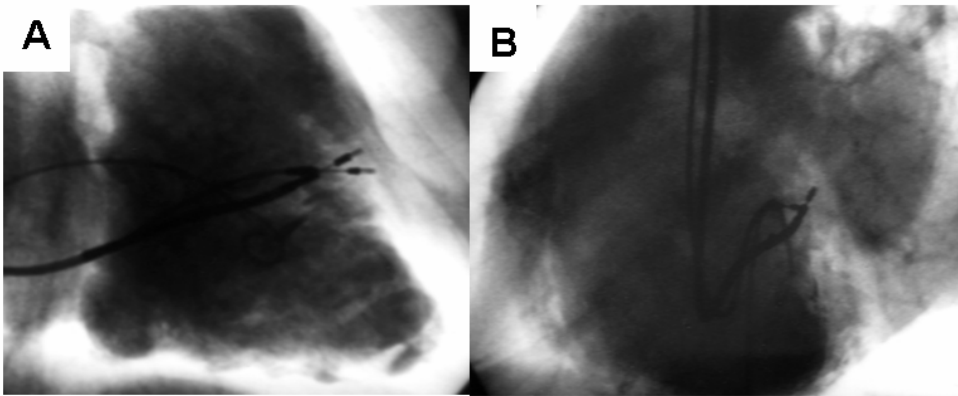


Figure 6. Right ventricular angiogram in 30° RAO (A) and 60° LAO (B) projections in a patient with ARVC and severe enlargement and dysfunction of the right ventricle. An atypical position of the RV defibrillation lead in the right ventricular outflow tract and an additional pace/sense lead were required to secure adequate sensing and pacing results in the severely diseased right ventricular myocardium.

During long-term follow-up of 80 ± 43 months after ICD-implantation in ARVC, we observed 53 adverse events in 37 of 60 patients (62%), including infection, malfunction or failure of the ICD-system. The majority of complications was related to insulation failure/oversensing, undersensing, fracture or thrombosis of the implanted leads and frequently required unscheduled surgical revision (37) (Figure 7). Similar complications were reported by other groups, however at a lesser rate due to the shorter follow-up periods (38-40).

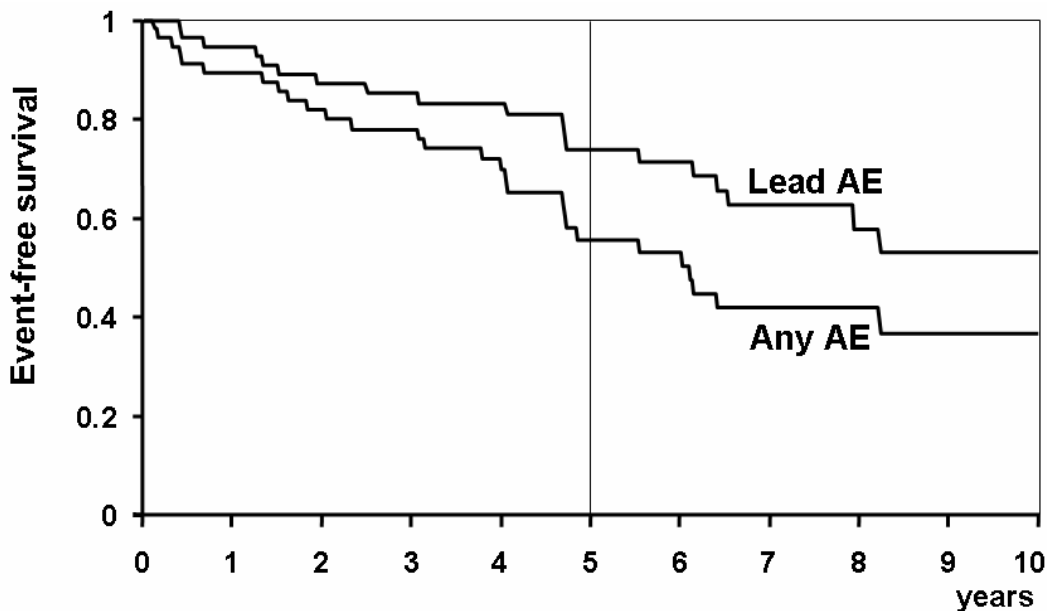


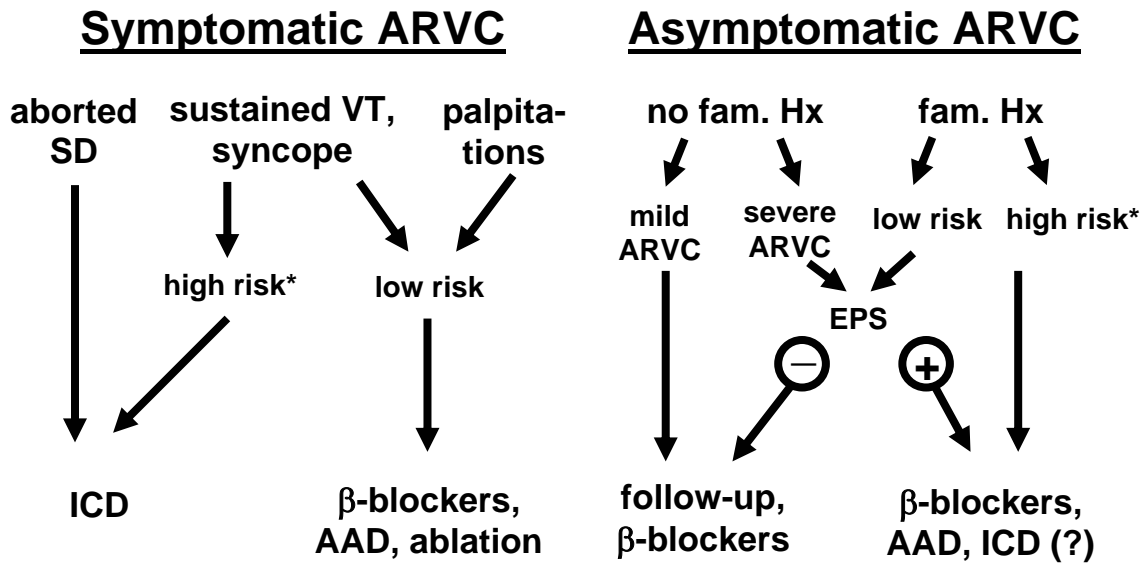


Figure 7. Complications during follow-up (80 ± 43 months) after ICD implantation in ARVC. Kaplan-Meier curves depict freedom of all adverse events (any AE) and lead-related complications (lead AE) (adapted from 37).

Therefore, the indication for ICD implantation in ARVC should weigh the potential benefit against the risk of complications. For secondary prevention in patients at high risk of sudden death, this relation is in strong favour for ICD therapy, because the published studies clearly demonstrated a significant benefit in survival. In primary prevention, however, the situation is less clear and more data are required to refine the selection of those patients with ARVC who benefit most from prophylactic ICD implantation.

Treatment Strategies to Prevent Sudden Cardiac Death

Different studies reported a 10-year overall mortality of 5% to 25% according to the treatment strategy applied. The limited data on risk stratification indicate that patients with severe right ventricular dysfunction, left ventricular involvement, a history of syncope or cardiac arrest, family history, inducible VT/VF and ECG abnormalities (epsilon potential, late potential) are more prone to life-threatening VT and sudden death. The best results with regard to long-term survival are achieved by individualized treatment strategies, including drug therapy, catheter ablation and ICD implantation. No prospective or randomised studies have investigated the comparative efficacy of these different treatment options so far. A proposal for current therapeutic management directed toward an improvement of symptoms and prognosis in patients with ARVC is depicted in Figure 8.



* Risk factors: severe RV dysfunction, LV involvement, hemodynamic unstable VT/VF, pleomorphic VT, epsilon potential, late potential, family history (SD, ARVC)

Figure 8. Proposed algorithm for the antiarrhythmic management of ARVC. (modified from 10)

AAD: antiarrhythmic drugs; EPS: electrophysiological study; fam. Hx: family history; ICD: implantable cardioverter-defibrillator; SD: sudden death; VT: ventricular tachycardia.

Management of asymptomatic patients and family members

Asymptomatic patients with ARVC do not require specific antiarrhythmic or otherwise cardiac treatment. However, they should be followed by regular noninvasive cardiac investigations for the early recognition of ventricular arrhythmias and the potential progression of the disease with worsening of global or regional myocardial dysfunction. These follow-up visits should include a detailed interview concerning the interim occurrence of arrhythmic symptoms or events, ECG at rest, exercise tests, Holter monitoring and cardiac imaging by echocardiography and/or magnetic resonance imaging. Patients with ARVC should be advised against participation in competitive sports since this appears to be associated with accelerated disease progression and increased risk of sudden death (10, 14)

Family members of patients with ARVC should visit a cardiologist experienced with the disease at regular intervals (3 to 5 years or with onset of symptoms). Modified diagnostic criteria for family members of affected index patients with ARVC were recently proposed but are not prospectively validated (42). 12-lead surface ECG and



echocardiography represent essential baseline diagnostic investigations which should be completed by exercise testing, Holter monitoring and signal-averaged ECG whenever possible and suitable. If these investigations show signs suspicious of ARVC or if complex ventricular arrhythmias are documented or syncope occurs, more detailed investigations should be performed to establish the diagnosis, to stratify the risk, and to develop an individualized treatment strategy. In affected but asymptomatic family members of ARVC patients, there is no general indication for prophylactic antiarrhythmic therapy. However, in patients with multiple risk factors, familial sudden death, or inducible VT during programmed stimulation, an empiric treatment with β -blockers or amiodarone, or the prophylactic implantation of an ICD may be discussed. Prophylactic ICD implantation has been performed in selected ARVC patients with a malignant family history for the primary prevention of sudden death. However, given the paucity of data, this approach is still controversial and requires an individual decision based on the specific constellation of risk.

Management of symptomatic patients

In patients with ARVC and symptomatic ventricular runs or premature ventricular beats, treatment with β -blockers should be considered, whereas specific antiarrhythmic drugs should be reserved for selected patients.

Patients with nonsustained and sustained VT or syncope should undergo a detailed diagnostic work-up to stratify the risk and to assess the inducibility of the clinical ventricular arrhythmia, both having an impact on the subsequent treatment strategy. In low-risk patients, antiarrhythmic drug therapy (preferentially sotalol) may be considered and should be guided by serial electrophysiologic study. In our experience, this approach showed favorable long-term results in selected low-risk patients with low rates of VT recurrence and sudden death. Catheter ablation may be an alternative option in patients with localized ARVC and a single morphology of a hemodynamically well tolerated VT refractory to antiarrhythmic drugs. In patients with drug-refractory frequent or incessant VT, catheter ablation may be the only treatment option available, however with a palliative claim.

Although antiarrhythmic drug therapy and catheter ablation may reduce VT recurrences, there is no proof from prospective or randomized studies, that they are also effective in the prevention of sudden death. Therefore, more effective protection is required in individuals at a high risk of sudden death. In patients with survived cardiac arrest or hemodynamically intolerable fast VT, and those with risk factors such as extensive right ventricular dysfunction, advanced stages of ARVC, left ventricular involvement, or pleomorphic VT, ICD implantation is considered the most appropriate therapeutic option to prevent life-threatening VT recurrences and sudden death.

Ongoing multicenter European (43) and North American (44) ARVC registries will provide important data on risk stratification and treatment efficacy which may refine the management strategies and thereby further improve the long-term prognosis of patients with ARVC.



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