JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER

VOL. 68, NO. 23, 2016
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2016.09.951

Arrhythmogenic Right Ventricular Cardiomyopathy

Clinical Course and Predictors of Arrhythmic Risk

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ABSTRACT

BACKGROUND Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a leading cause of sudden cardiac death, but its progression over time and predictors of arrhythmias are still being defined.

OBJECTIVES This study sought to describe the clinical course of ARVC and occurrence of life-threatening arrhythmic events (LAE) and cardiovascular mortality; identify risk factors associated with increased LAE risk; and define the response to therapy.

METHODS We determined the clinical course of 301 consecutive patients with ARVC using the Kaplan-Meier method adjusted to avoid the bias of delayed entry. Predictors of LAE over 5.8 years of follow-up were determined with Cox multivariable analysis. Treatment efficacy was assessed comparing LAE rates during matched time intervals.

RESULTS A first LAE occurred in 1.5 per 100 person-years between birth and age 20 years, in 4.0 per 100 person-years between ages 21 and 40 years, and in 2.4 per 100 person-years between ages 41 and 60 years. Cumulative probability of a first LAE at follow-up was 14% at 5 years, 23% at 10 years, and 30% at 15 years. Higher risk of LAE was predicted by atrial fibrillation (hazard ratio [HR]: 4.38; $p = 0.002$), syncope (HR: 3.36; $p < 0.001$), participation in strenuous exercise after the diagnosis (HR: 2.98; $p = 0.028$), hemodynamically tolerated sustained monomorphic ventricular tachycardia (HR: 2.19; $p = 0.023$), and male sex (HR: 2.49; $p = 0.012$). No difference was observed in the occurrence of LAE before and after treatment with amiodarone, beta-blockers, sotalol, or ablation. A total of 81 patients received an implantable cardioverter-defibrillator, 34 were successfully defibrillated.

CONCLUSIONS The high risk of life-threatening arrhythmias in patients with ARVC spans from adolescence to advanced age, reaching its peak between ages 21 and 40 years. Atrial fibrillation, syncope, participation in strenuous exercise after the diagnosis of ARVC, hemodynamically tolerated sustained monomorphic ventricular tachycardia, and male sex predicted lethal arrhythmias at follow-up. The lack of efficacy of antiarrhythmic therapy and the life-saving role of the implantable cardioverter-defibrillator highlight the importance of risk stratification for patient management. (J Am Coll Cardiol 2016;68:2540–50) © 2016 by the American College of Cardiology Foundation.

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Manuscript received April 6, 2016; revised manuscript received September 8, 2016, accepted September 9, 2016.

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited disease (1) characterized by progressive replacement of the myocardium by adipose and fibrous tissue (2) that predisposes to development of ventricular tachycardia (VT) and to sudden cardiac death (SCD). This condition was described 3 decades ago, when fibrofatty infiltration in the right ventricle was considered its pivotal indicator (3,4). It later became clear that ARVC is mainly caused by mutations in the genes encoding for desmosomal proteins (1). This helped establish that the disorder is often associated with biventricular manifestations (5), and the term *arrhythmogenic cardiomyopathy* has also been proposed (1). The unmet need in managing patients with ARVC is represented by the lack of an evidence-based scheme to identify individuals who are at high risk of SCD.

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Here we present data on the clinical course of patients with ARVC from our registry, highlighting the importance of behavioral risk factors in disease progression, and providing information that may affect clinical management. In describing the clinical manifestations of ARVC in our cohort, we adopted a different statistical approach from the one used by previous studies: we took into account the survivorship bias inherent in studying populations who are not followed-up since birth (6), which might have generated overly optimistic conceptions about ARVC severity.

We also report data on the risk predictors for the first life-threatening arrhythmia occurring during a median observation time of 5.8 years, and describe the effect of antiarrhythmic drugs, transcatheter ablation, and implantable cardioverter-defibrillators (ICDs) on the prognosis of patients with ARVC.

METHODS

A list of the definitions used (Online Table 1) and a detailed description of the clinical assessment and management of patients and of the genetic screening performed are in the Online Appendix.

AIMS AND ENDPOINTS. There were 3 aims to our study. First, we sought to describe the clinical course of ARVC, assessing the occurrence of a first life-threatening arrhythmic event (LAE) defined as SCD, aborted cardiac arrest, syncopal VT or electrical storm, or cardiovascular mortality. At variance with prior studies that examined predictors of any sustained ventricular arrhythmia or "malignant" ventricular arrhythmias (cycle length <240 ms), we selected a novel endpoint.

Second, we evaluated the occurrence of LAE at follow-up and sought to identify predictors of the first LAE.

Finally, we worked to define the response to therapy at follow-up.

STATISTICAL ANALYSIS. Statistical analysis was performed using SPSS version 21 (IBM Corporation, Armonk, New York) and R version 3.0 (R Foundation, Vienna, Austria). Data are expressed as percentage, mean ± SD, or median with interquartile range (IQR) for skewed distributions.

Previous studies have described the "natural history" of ARVC by applying the Kaplan-Meier analysis to the time interval between birth and last follow-up (7,8). This approach, albeit widely used, is methodologically flawed as it overestimates survival probability. Patients diagnosed with ARVC at older ages, by virtue of having survived to the time of diagnosis, could not have had an event between birth and the time of diagnosis. This phenomenon, called delayed entry or left-truncation, is common in studies where the time variable of interest is the age of an individual. To avoid this bias, we removed patients from the risk set between birth and diagnosis of ARVC, and considered only the time during which patients were followed prospectively. For this reason, 15 patients who experienced SCD as the first manifestation of ARVC and 8 patients lost to follow-up were not included in the analysis. The survival function was estimated using the adjusted Kaplan-Meier estimator proposed by Tsai et al. (6). Considering that the youngest patient included in the analysis was 1.9 years of age at the beginning of observation and that the probability of experiencing an LAE related to ARVC in early infancy is deemed to be extremely low (9,10), we described the clinical manifestations of our cohort from birth.

To highlight the behavior of ARVC in different age groups, we reported incidence rates for LAE and for cardiovascular mortality according to the following categories: from birth to age 20 years, from age 21 to 40 years, and from age 41 to 60 years.

Incidence rates were computed by dividing the number of patients experiencing a first LAE or cardiovascular death by the total number of person-years. Also, to adjust for delayed entries, the time from birth to diagnosis was not considered in the person-years calculation.

During follow-up, we recorded LAE occurrence both in patients who presented for medical attention after surviving an LAE with documented ventricular fibrillation (VF) (n = 11) and in those

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

ARVC = arrhythmogenic right ventricular cardiomyopathy

HT-MMVT = hemodynamically tolerated sustained monomorphic ventricular tachycardia

ICD = implantable cardioverter-defibrillator

IQR = interquartile range

LAE = life-threatening arrhythmic event

SCD = sudden cardiac death

VF = ventricular fibrillation

VT = ventricular tachycardia

TABLE 1 Phenotypic Characteristics of 301 ARVC Patients at First Visit*

Demographics	
Male	58
Age, yrs	38 ± 18
Clinical manifestations at presentation	
Life-threatening arrhythmic event	8.6
Syncope	9.3
Hemodynamically tolerated sustained monomorphic VT	13.2
Atrial fibrillation	3.3
NYHA functional class ≥II	1.0
12-lead ECG (85% of patients)	
PR interval duration, ms	159 ± 26
QRS duration in V_1, ms	95 ± 18
QRS fragmentation V_1 to V_3	16
Epsilon wave	5
Terminal S-wave ≥55 ms V_1–V_3	35
T-wave inversion V_1–V_3	35
Holter monitoring (72% of patients)	
NSVT	32
VEB >500/24 h	52
VEB burden/24 h, n	2.617 ± 5.180
Exercise stress test (62% of patients)	
NSVT	15
SA-ECG (40% of patients)	
Late potentials: ≥1 positive	64
Late potentials: 3 of 3 positive	16
Magnetic resonance imaging (62% of patients)	
RV RWMA abnormalities	41
RV EDV indexed, ml/m^2	87 ± 24
RV EF, %	53 ± 12
RV fatty infiltration	27
LV RWMA abnormalities	9
LV EDV indexed, ml/m^2	81 ± 19
LV EF, %	61 ± 8
LV fatty infiltration	7
LGE on LV or RV or both	31
Transthoracic echocardiogram (76% of patients)	
RV RWMA abnormalities	9
RV EDD-PLAX indexed, mm/m^2	17 ± 4
RV EDD-PSAX indexed, mm/m^2	17 ± 3
FAC <33%	8
LV RWMA abnormalities	1
LV EDD indexed, mm/m^2	27 ± 3
LV EF, %	61 ± 7
Endomyocardial biopsy (6% of patients)	
Fibro-fatty substitution of myocardium	56
RV angiography (14% of patients)	
Regional RV akinesia, dyskinesia, or aneurysm	21
Electrophysiological study (31% of patients)	
Inducibility of sustained VT/VF	38
Presence of low voltages on endocardial mapping	58

Values are % or mean ± SD. *Parameters are defined in accordance with the 2010 Task Force Criteria (13).

ECG = electrocardiogram; EDD = end-diastolic diameter; EDV = end-diastolic volume; EF = ejection fraction; FAC = fractional area change; LGE = late gadolinium enhancement; LV = left ventricle/ventricular; NSVT = nonsustained ventricular tachycardia; NYHA = New York Heart Association; PLAX = parasternal long-axis diameter; PSAX = parasternal short-axis diameter; RV = right ventricle/ventricular; RWMA = regional wall motion abnormalities; SA-ECG = signal-averaged electrocardiogram; VEB = ventricular extrasystolic beats; VF = ventricular fibrillation; VT = ventricular tachycardia.

without a previous LAE (n = 267). Because the first group of individuals already had a Class I indication for an ICD (11), the predictors of LAE at follow-up were assessed in the second group. The cumulative probability of a first LAE during follow-up was determined with the life-table method of Kaplan-Meier, and results were compared with the log-rank test. Patients were censored at last visit or at the occurrence of death for nonarrhythmic causes. Prognostic factors for LAE at follow-up were assessed by univariable analysis and listed in the Online Appendix.

Characteristics significantly ($p < 0.05$) or nearly significantly ($p < 0.10$) associated with LAE in the univariable analysis were first entered as candidate variables in a multivariable Cox proportional hazards regression analysis. The final multivariable model was selected using a backward-elimination algorithm (retention threshold $p < 0.05$).

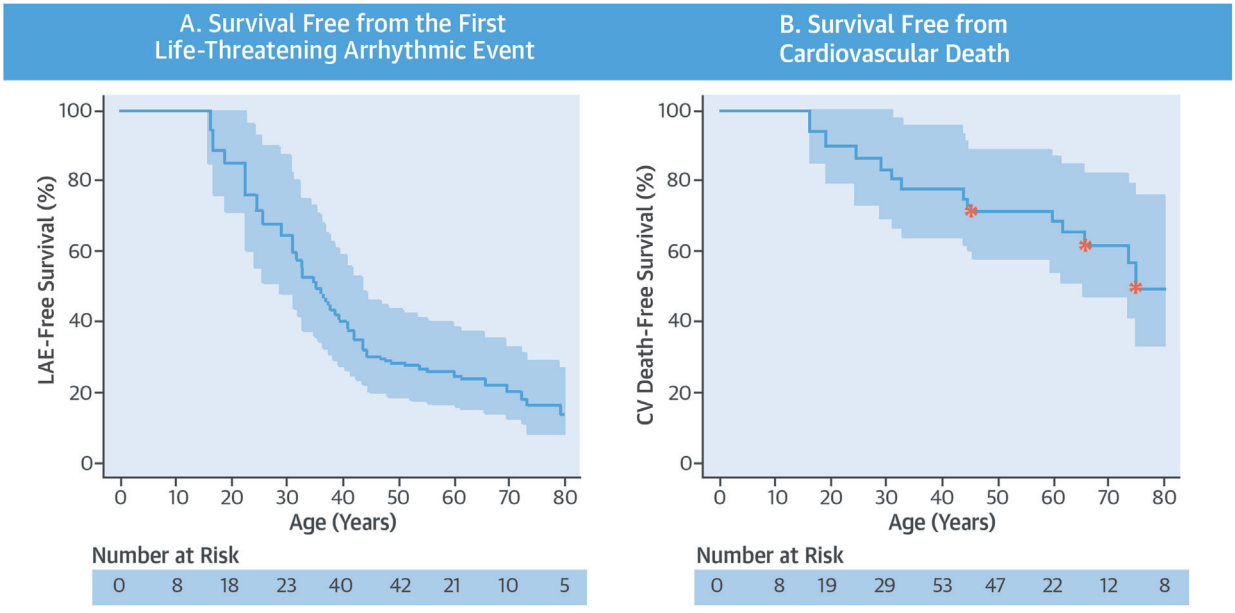
To assess efficacy of antiarrhythmic therapy, we compared matched periods before and after administration of the first antiarrhythmic drug (sotalol, amiodarone, or beta-blockers), with patients serving as their own controls. LAE incidence rates were calculated by dividing the number of events by person-years of follow-up within each matched period. The same approach was applied to compare the rates of LAE before and after the first catheter ablation. The comparison was on the basis of the results of a Poisson regression model. Robust standard errors were computed using generalized estimating equations to account for intrapatient correlation. In all analyses, $p < 0.05$ was considered statistically significant.

RESULTS

Between January 1999 and May 2014, 273 probands were referred to our center for a suspicion of ARVC, and in 163 the diagnosis was established on the basis of the diagnostic criteria enforced at the time of their first presentation (12,13). Before enrollment in the present study, the diagnosis was confirmed using the 2010 Task Force Criteria (13). Of the 163 families, 110 accepted screening of family members, and 326 individuals were evaluated. One or more affected relatives were identified in 70 of 110 families (64%). Overall, 138 of 326 (42%) relatives were diagnosed with ARVC, totaling 301 patients in our registry (Table 1).

A total of 43 probands (26%) had a family history of unexplained sudden death and 18 (11%) had multiple victims in the family (median 2; IQR: 2 to 3); a total of

CENTRAL ILLUSTRATION **Clinical Course of ARVC**



Mazzanti, A. et al. J Am Coll Cardiol. 2016;68(23):2540–50.

The high risk of life-threatening arrhythmias **(A)** in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC) spans from adolescence to advanced age, reaching its peak between the third and the fourth decade of life. The risk of cardiovascular (CV) death **(B)** is constant in all age groups. **Orange asterisks** indicate patients who died from end-stage heart failure; **light blue shading** indicates confidence intervals of the curves. LAE = life-threatening arrhythmic event.

65 sudden death victims were identified in 43 families (44 males [68%]; age at death 43 ± 18 years).

Overall, 73 of 301 patients (54 men [74%]) experienced 1 or more LAE (age at first LAE 39 ± 15 years); 39 of 73 (53%) patients had been asymptomatic before experiencing their LAE. At first LAE, 26 of 73 (35.5%) patients died, 15 (20.5%) were defibrillated by paramedics, and 32 (44%) were treated successfully by their ICD. A total of 23 of 47 (49%) patients surviving a first LAE had multiple LAEs during their life (median 2; IQR: 2 to 3).

A total of 31 cardiovascular deaths occurred in our cohort: 27 SCDs at 37 ± 16 years, 3 deaths from end-stage heart failure at age 61 ± 15 years, and 1 death from stroke at 85 years. Another 4 patients died from noncardiovascular causes at age 83 ± 4 years.

Results of genetic screening are reported in the Online Appendix.

CLINICAL COURSE. The cumulative probability of experiencing a first LAE during lifetime (**Central Illustration**, panel A) was 14.6% (95% confidence interval [CI]: 0.0% to 29.3%), 59.5% (95% CI: 41.0% to 73.2%), and 74.8% (95% CI: 61.2% to 84.4%) at 20, 40, and 60 years, respectively. The rate of occurrence of a first LAE was calculated in 267 patients using the Kaplan-Meier method corrected for left-truncation. The rate of occurrence of a first LAE was 1.5 per 100 person-years between birth and age 20 years, 4.0 per 100 person-years between age 21 and 40 years, and 2.4 per 100 person-years between age 41 and 60 years (**Table 2**). These data demonstrated that from mid-adolescence, LAEs begin to occur with a clinically relevant incidence.

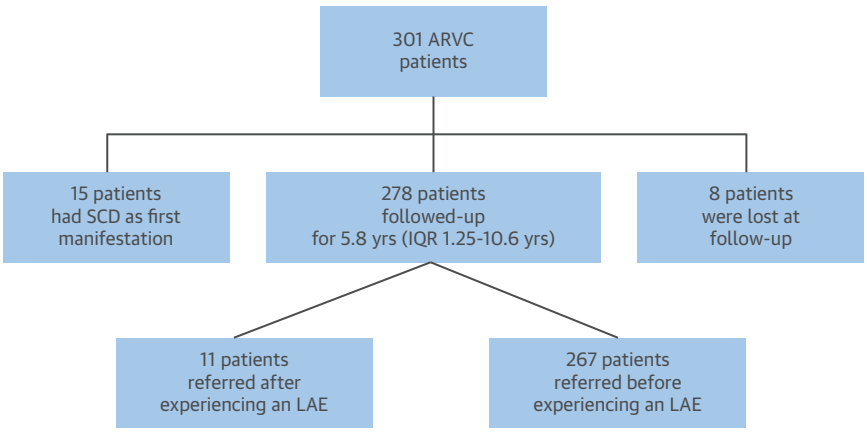
The cumulative probability of cardiovascular mortality calculated with the Kaplan-Meier method corrected for left-truncation was 9.3% (95% CI: 0.0% to 21.3%), 21.9% (95% CI: 4.5% to 36.7%), and 31.1% (95% CI: 13.2% to 46.1%) at 20, 40, and 60 years, respectively (**Central Illustration**, panel B). The overall

TABLE 2 **Incidence Rates of Life-Threatening Arrhythmias and of Cardiovascular Mortality**

	0-20 Yrs	21-40 Yrs	41-60 Yrs
Life-threatening arrhythmias	1.5*	4.0	2.4
Cardiovascular mortality	1*	0.6	0.6

Values are incidence rates of the first life-threatening arrhythmia and of cardiovascular mortality expressed as value per 100 person-years in different age groups. *Caution is required in interpreting these numbers because they are based on a small number of patients followed-up since a young age.

FIGURE 1 Follow-Up Data



Of the 301 patients included in the database, 15 had sudden cardiac death (SCD) as the first symptom of arrhythmogenic right ventricular cardiomyopathy (ARVC) and 8 were lost to follow-up. The remaining 278 patients were followed-up for a median time of 5.8 years: 11 were referred after surviving a life-threatening arrhythmic event (LAE), whereas 267 did not experience an LAE before observation. IQR = interquartile range.

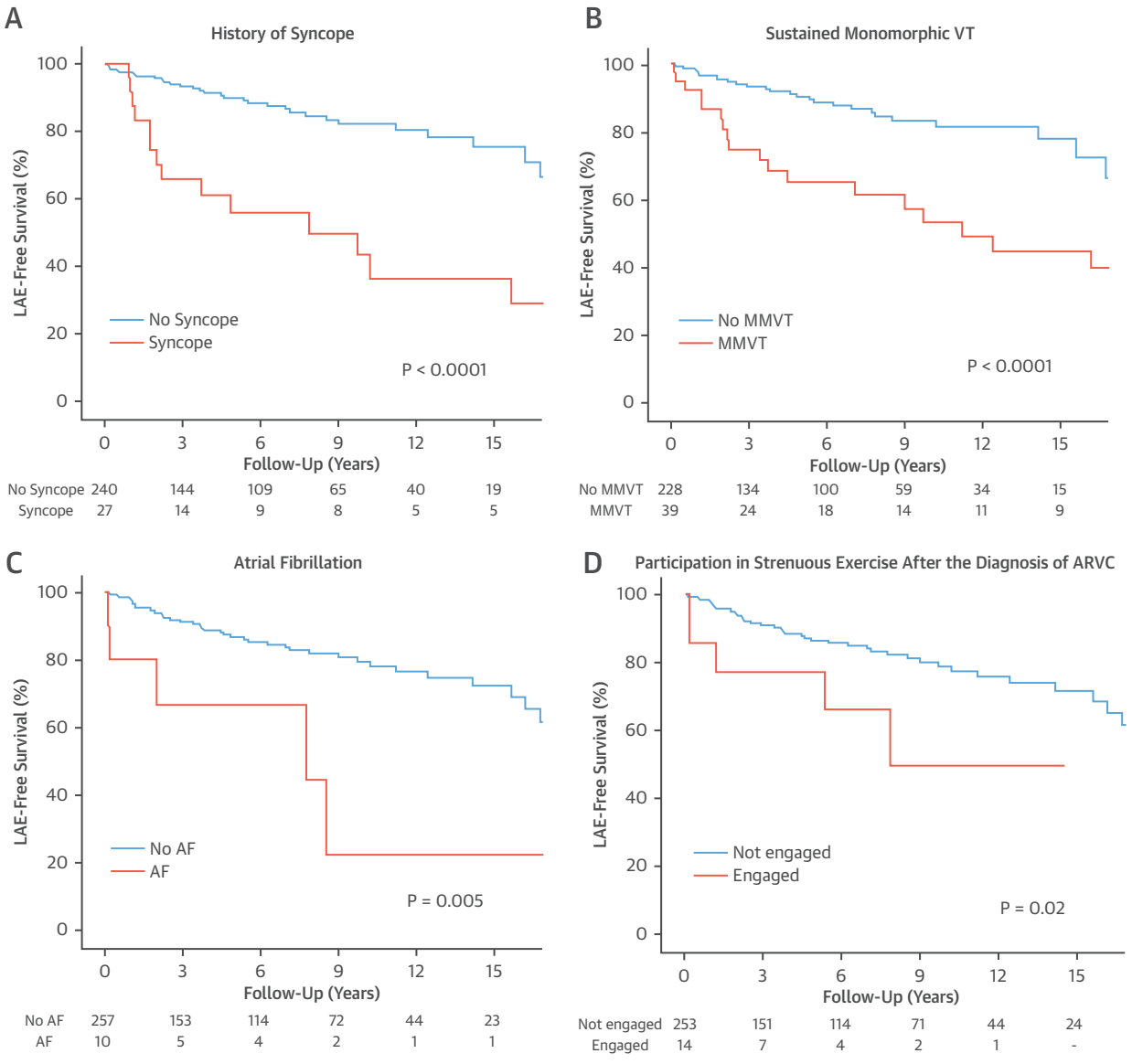
annual rate of cardiovascular mortality was 0.8 per 100 person-years. The rate of occurrence of cardiovascular mortality was 1 per 100 person-years between birth and 20 years and 0.6 per 100 person-years both in the age 21 to 40 years and 41 to 60 years groups (**Table 2**).

FOLLOW-UP. Of the 301 patients in the database, 15 experienced SCD as the first manifestation of the disease and 8 were lost to follow-up; thus, observational data were available for 278 patients (**Figure 1**, Online Figure 1), who were followed for a median of 5.8 years (IQR: 1.25 to 10.6 years). Over this period, 49 of 278 (17.6%) patients had a first LAE, with an incidence of 2.7 per 100 person-years (49 first events over 1,789 person-years).

When focusing on the 267 patients who did not experience an LAE before the first visit, we observed that during a median follow-up of 5.8 years (IQR: 1.3 to 10.6 years), 47 patients had a first LAE (47 first events in 267 patients over 1,700 person-years for an incidence rate of 2.8 per 100 person-years). The cumulative probability of a first LAE during follow-up was 14% at 5 years, 23% at 10 years, and 30% at 15 years (Online Figure 2). Univariable analysis found that male sex ($p = 0.003$), age at observation between 21 and 40 years ($p < 0.0001$), history of syncope ($p < 0.0001$), history of hemodynamically tolerated sustained monomorphic ventricular tachycardia (HT-MMVT) ($p < 0.0001$), history of atrial fibrillation (AF) ($p = 0.005$), proband status ($p = 0.001$), and participation in strenuous exercise after the diagnosis ($p = 0.02$) were associated with LAE occurrence during follow-up (**Figure 2**, Online Figure 3). Conversely, neither a family history of sudden death ($p = 0.872$) nor any electrocardiographic parameter (Online Figure 4) were predictive. Cox multivariable analysis showed a significant and independent increase in the risk of LAE associated with history of AF, history of syncope, participation in strenuous exercise after the diagnosis, history of HT-MMVT, and male sex (**Table 3**). Interestingly, the significance of "proband status" at univariable analysis was not retained in the multivariable model due to its strong correlation with the history of syncope and history of HT-MMVT (25 of 27 patients with syncope and 37 of 39 patients with history of HT-MMVT were also probands).

A total of 11 patients (6 males [54%]) arrived at medical attention after surviving an LAE: only 1 patient had a syncopal event before experiencing cardiac arrest, whereas the remainder were asymptomatic. According to international guidelines, all patients had indications for ICD implantation (11), which was accepted by 9 of them and refused by a 17-year-old girl and a 59-year-old man. During a median follow-up of 9.2 years (IQR: 2.7 to 10.1 years), 2 males (ages 28 and 34 years at presentation) had a second LAE, despite beta-blocker therapy (2 first events in 11 patients over 89 person-years; incidence rate: 2.2 per 100 person-years). Both of these patients had an ICD

FIGURE 2 **Life-Threatening Arrhythmic Events at Follow-Up**



Kaplan-Meier estimate of cumulative survival free from the first LAE during follow-up varied significantly by presence or absence of **(A)** history of syncope, **(B)** sustained monomorphic ventricular tachycardia, **(C)** atrial fibrillation (AF), and **(D)** participation in strenuous exercise after the diagnosis, evaluated at presentation in 267 patients who did not present with an LAE. LAE = life-threatening arrhythmic event; MMVT = sustained monomorphic ventricular tachycardia; VT = ventricular tachycardia.

implanted: the first experienced an arrhythmic storm and was not saved by the device, whereas the second had an episode of VF interrupted by an appropriate shock.

DRUG THERAPY, CATHETER ABLATION, AND ICD. In our population 119 patients (76 males [64%]) received at least 1 antiarrhythmic agent (sotalol, amiodarone, or beta-blockers) empirically used to prevent arrhythmias in ARVC (11). The median time on drug therapy was 3.5, 3.5, and 2 years for sotalol, amiodarone, and beta-blockers, respectively. We compared the occurrence of LAE in matched periods before and after therapy: none of the drugs significantly reduced the rate of LAE at multivariable analysis (**Table 4**, Online Table 2).

A total of 27 patients (18 males [67%]) underwent ≥1 catheter ablations (24 patients only

TABLE 3 Predictors of Arrhythmic Risk at Follow-Up

Risk Factor	Univariable Analysis*			Multivariable Analysis*		
	β (SE)	HR (95% CI)	p Value†	β (SE)	HR (95% CI)	p Value
Male	1.01 (0.36)	2.76 (1.37–5.56)	0.005	0.91 (0.36)	2.49 (1.22–5.07)	0.012
Family history of unexplained sudden death	−0.05 (0.30)	0.95 (0.52–1.73)	0.872	–	–	–
Atrial fibrillation	1.26 (0.48)	3.51 (1.38–8.93)	0.008	1.48 (0.48)	4.38 (1.70–11.29)	0.002
History of syncope	1.51 (0.31)	4.54 (2.48–8.34)	<0.001	1.21 (0.34)	3.36 (1.71–6.60)	<0.001
History of HT-MMVT	1.21 (0.30)	3.37 (1.87–6.07)	<0.001	0.79 (0.35)	2.19 (1.12–4.32)	0.023
Participation in strenuous exercise	1.06 (0.48)	2.90 (1.14–7.38)	0.026	1.09 (0.50)	2.98 (1.12–7.90)	0.028
Age at presentation ≤20 yrs vs. >40 yrs	−0.36 (0.57)	0.70 (0.23–2.14)	0.530	–	–	–
Age at presentation 21–40 yrs vs. >40 yrs	1.07 (0.33)	2.91 (1.51–5.58)	0.001	–	–	–
Proband status‡	1.26 (0.39)	3.54 (1.65–7.59)	0.001	–	–	–
Negative T waves in leads V_1–V_3	0.48 (0.31)	1.62 (0.88–2.99)	0.121	–	–	–
Nonsustained VT	0.34 (0.30)	1.40 (0.78–2.51)	0.256	–	–	–
PVC count >1,000/day	0.01 (0.39)	1.01 (0.47–2.18)	0.984	–	–	–

*Estimates from univariable and multivariable Cox regression models predicting life-threatening arrhythmic events after presentation in 267 patients who did not present with an LAE. †p values differ slightly from those presented in Figure 3 and in Online Figures 3 and 4 due to the use of the Wald test based on Cox regression models as opposed to the log-rank test statistic. ‡The significance of "proband status" at univariable analysis was not retained in the multivariable model, due to its strong correlation with the history of syncope and the history of HT-MMVT (25 of 27 patients with syncope and 37 of 39 patients with HT-MMVT were also probands).

CI = confidence interval; HR = hazard ratio; HT-MMVT = hemodynamically tolerated sustained monomorphic ventricular tachycardia; PVC = premature ventricular contraction; SE = standard error; other abbreviations as in Table 1.

endocardial ablations, 2 endocardial and epicardial ablations, and 1 only epicardial ablation); before the procedure, 7 had survived an LAE, 11 had experienced ≥1 HT-MMVT, and 9 had remained asymptomatic but had documented nonsustained VT and/or frequent ventricular extra systolic beats. A total of 9 patients (33%) underwent multiple procedures (3 ± 1 each; range 1 to 5) after 6 months (IQR: 4 to 14 months) from the first ablation. Following ablation, 16 of 27 (59%) patients had ≥1 sustained VT 2 years post-procedure (IQR: 0.33 to 4.83 years), with an incidence rate of 17 per 100 person-years. Of these, 5 had survived a previous LAE, 8 had experienced ≥1 HT-MMVT, and 3 were symptom free. Importantly, 12 of these 16 patients experienced a first LAE (2 ± 1; range: 1 to 4) 2.9 years post-procedure (IQR: 1.90 to 4.83 years), with an incidence rate of 12 per 100 person-years. LAE rate in matched periods during a median 4.8 years before and after catheter ablation was not significantly different (p = 0.644) (Table 4).

TABLE 4 Matched-Periods Analysis for the Efficacy of Antiarrhythmic Drugs and Transcatheter Ablation*

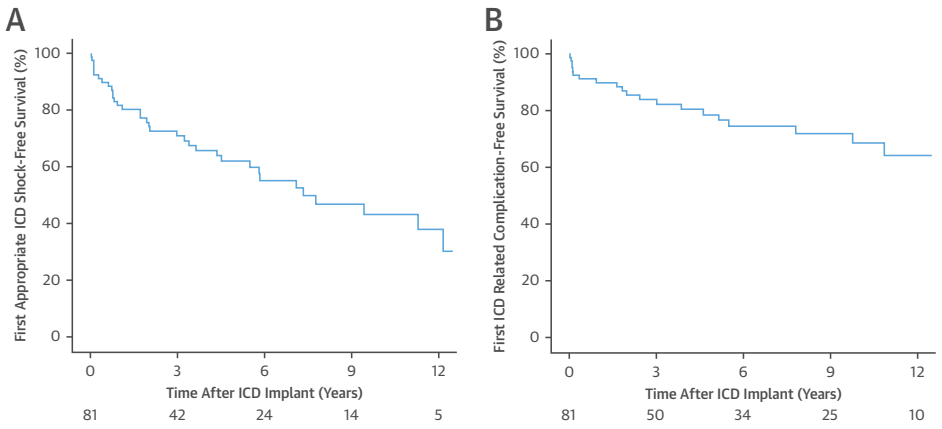
Treatment	Time	n	Person-Yrs	LAE	Rate	95% CI	p Value
Beta-blockers†	Before	67	218	7	0.032	0.015–0.068	0.107
	After	67	218	15	0.069	0.033–0.145	
Sotalol	Before	37	220	3	0.014	0.003–0.060	0.062
	After	37	220	16	0.073	0.030–0.178	
Amiodarone	Before	15	88	1	0.011	0.002–0.083	0.048
	After	15	88	9	0.102	0.047–0.223	
Ablation	Before	27	170	16	0.094	0.035–0.253	0.644
	After	27	170	20	0.117	0.069–0.200	

*Matched-periods analysis shows the event-rates per 100 person-years before/after treatment with the first antiarrhythmic drug administered and before/after the first catheter ablation. †Dosages of individual beta-blockers: metoprolol (n = 24: 95 ± 62 mg/day); atenolol (n = 15: 65 ± 36 mg/day); bisoprolol (n = 14: 5 ± 3 mg/day); nadolol (n = 7: 33 ± 23 mg/day); nebivolol (n = 3: 3 ± 2 mg/day); propranolol (n = 2: 82 ± 23 mg/day); and carvedilol (n = 2: 38 ± 18 mg/day).

Abbreviations as in Tables 1 and 3.

A total of 81 patients (55 males, age at first implant 42 ± 15 years) received an ICD (13 after and 68 before experiencing an LAE; criteria for ICD implantation and details for ICD programming are in Online Figures 5 and 6, Online Table 3, and related legends), and at follow-up, 35 (43%) experienced an LAE triggering an appropriate shock that successfully terminated the arrhythmic event in 34 (97%). The device did not save 1 patient experiencing an arrhythmic storm. A total of 26 (74%) of these 35 patients who experienced appropriate ICD interventions on LAE were receiving antiarrhythmic therapy at the time of the event (12 taking beta-blockers, 9 sotalol, and 5 amiodarone), and 7 (20%) had undergone catheter ablation before ICD implant. In patients with an ICD, neither antiarrhythmic drug therapy nor a previous catheter ablation were associated with an improved shock-free survival (p = 0.775 for drugs; p = 0.061 for ablation). The cumulative probability of an appropriate shock was 18%, 24%, and 57% at 1, 2, and 10 years, respectively (Figure 3A). Patients implanted after experiencing either syncope or HT-MMVT had an almost 3-fold increased probability of being defibrillated than asymptomatic patients (HR: 2.71; 95% CI: 1.23 to 5.92; p = 0.013).

FIGURE 3 **Implantable Cardioverter Defibrillators: Appropriate Shocks and Complications**



Kaplan-Meier estimate of cumulative survival free from **(A)** the first appropriate implantable cardioverter-defibrillator (ICD) shock triggered by a life-threatening arrhythmic event (LAE) and **(B)** first ICD-related complication (inappropriate shock in 17 and device/lead dysfunction in 3 of 20 patients). Abbreviations as in **Figure 1**.

Patients with an ICD had a higher LAE rate than patients who were treated with antiarrhythmic drugs (HR: 9.7; 95% CI: 5.29 to 17.70; $p < 0.0001$) (Online Table 2). This observation might be the consequence of the fact that patients implanted with an ICD represent a high-risk subgroup (Online Table 3). Interestingly, when we compared SCD occurrence in patients with versus without an ICD, we failed to observe any difference in arrhythmic mortality in implanted versus nonimplanted patients (HR: 0.32; 95% CI: 0.04 to 2.45; $p = 0.26$) (Online Figure 7).

ICD-related complications occurred in 20 of 81 (25%) patients in the first 1.9 years (IQR: 0.1 to 5.0 years) post-implantation (**Figure 3B**). In 17 patients, the first complication was an inappropriate shock secondary to sinus or supraventricular tachycardia ($n = 14$), lead dysfunction ($n = 2$), or T-wave oversensing ($n = 1$); in the remaining 3, it was a malfunction requiring implant revision. The cumulative probability of a first complication was 9%, 13%, and 28% at 1, 2, and 10 years, respectively. Overall, looking at all events at follow-up, 5 of 81 (6.1%) patients had major complications requiring the revision of the implant over 7 years (IQR: 2.3 to 11.0 years) of observation.

DISCUSSION

The description of disease progression over time (clinical course) contributes greatly to the understanding of rare disorders because it may facilitate the diagnostic process, guide risk stratification, and contribute to genetic counseling (14). Descriptions of the clinical course of cohorts of patients with inherited arrhythmogenic conditions, such as Brugada syndrome (15) and long-QT syndrome (16), have provided data on disease progression and risk factors that have influenced clinical practice guidelines in the last decade (17). The description of the occurrence of arrhythmic events between birth and the last observation in patients with ARVC has been described in different studies (7,8). In previous studies, however, data were analyzed using the Kaplan-Meier survival estimator, despite including data between birth and first clinical visit that were obtained by retrospectively analyzing the clinical history rather than through prospective clinical observation. Although this approach has been largely applied in the published data, it generates a survivorship bias that may underestimate severity of the investigated disease. To avoid this bias, we analyzed data on the clinical course of our patients by applying an adequate correction described earlier that includes only the period in which participating individuals were actually observed.

The behavior of ARVC in our population showed that the first LAE was seldom observed before the teenage years, as no events occurred before age 16 and the mean age at first LAE was 39 ± 15 years. Interestingly, we observed that the risk of experiencing an LAE is highest between 21 and 40 years, with a rate of first LAE occurrence of 4.0 per 100

person-years. In contrast, the risk of experiencing cardiovascular death was not different across the age groups, showing an annual rate of 0.8 per 100 person-years between birth and age 60 years. Our data add a new epidemiological perspective to the common belief that ARVC is "a disease of the young adult" (18) and show that in the teenage years the risk of developing life-threatening arrhythmias increases rapidly. This observation supports the rationale that in families with ARVC children should be screened when they approach adolescence. There are currently no data to determine the frequency of the screening, although screening at 2- to 3-year intervals seems reasonable.

PREDICTORS OF LAE RISK AT FOLLOW-UP. ARVC's clinical course helps to better characterize the behavior of the "average" patient with ARVC, but does not provide information to perform a personalized risk assessment.

According to the guidelines, patients with ARVC who experienced VF or have hemodynamically not tolerated VT have a Class I recommendation for ICD implantation (12); therefore, their management is straightforward.

The principal clinical challenge is to identify individuals who are at the highest risk of developing a first LAE after diagnosis in the absence of any evidence-based risk stratification scheme. A recent consensus document on managing patients with ARVC has highlighted the need to obtain more data on long-term prognosis to better profile high-risk individuals who may benefit from an ICD (19). In our population, the independent predictors of a first LAE at follow-up were history of syncope or HT-MMVT, documentation of AF, participation in strenuous exercise after the diagnosis, and male sex. As a word of caution, it should be noted that our population is representative of patients with an arrhythmic phenotype, as it includes <10% of patients with ventricular dysfunction at presentation (**Table 1**).

The occurrence of syncope is a common risk predictor in all inherited arrhythmias spanning from long-QT syndrome (20), to Brugada syndrome (21), and to catecholaminergic polymorphic VT (22). Although various substrates commonly manifest syncope, it remains a powerful indicator of arrhythmic risk in inherited arrhythmias. Interestingly, the presence of a syncopal event is more informative in identifying subjects who are at risk of major arrhythmic events than the presence of HT-MMVT. Our data, identifying syncope as a strong predictor of events in patients without a previous LAE (HR: 3.36), add to the debate on syncope's predictive role in ARVC: Corrado et al. (23) highlighted the key role of syncope in predicting arrhythmic events, whereas the study by Bhonsale et al. (24) did not confirm syncope's role as a risk stratifier in ARVC.

AF is known to be more frequent among patients with ARVC than in the general population (25), but its predictive role in ARVC has never been reported. In our cohort, AF increased the risk of LAE 4-fold, but its contribution to risk stratification is limited, as only 10 of 267 patients manifested AF. We investigated whether patients with AF in our cohort had more advanced structural abnormalities (e.g., reduced ejection fraction of right and/or left ventricles or atrial enlargement) or a higher prevalence of desmosomal mutations compared with patients without AF. We failed to demonstrate an association of AF with structural abnormalities ($p = 0.983$ for right ventricular ejection fraction; $p = 0.966$ for left ventricular ejection fraction; $p = 0.54$ for right atrial enlargement; $p = 0.34$ for left atrial enlargement; and $p = 0.25$ for tricuspid regurgitation) or with desmosomal mutations ($p = 0.112$). In fact, more than one-half of our patients with AF at presentation had a structurally normal heart when the arrhythmia occurred, including normal atrial size. We speculated that AF might reflect the presence of electrical instability, suggesting that atrial involvement may be a surrogate marker of a more severe predisposition to arrhythmias.

We were very interested in assessing the role of participation in strenuous exercise as a predictor of adverse outcome, as recently suggested (26). Our data showed that patients who engaged in strenuous exercise after ARVC diagnosis were at higher risk of events compared with patients who did not participate in intense physical training. This information is particularly relevant in Italy and other countries that have pre-participation screening of athletes. The evidence that sport increases the risk of life-threatening events by almost 3-fold provides a strong rationale to institute a program for early detection of ARVC in young athletes. These data, combined with the evidence that the teenage years represent the time at which LAE manifests in patients with ARVC, suggest that screening for ARVC around age 11 or 12 years may serve to both identify affected young individuals and prevent them from engaging in competitive sports.

As previously reported (8,19), males were at increased risk of experiencing an LAE during follow-up; it is unclear whether this sex-related difference in outcome depends on increased engagement in athletic activities by men or whether sex hormones play a role.

It is important to consider that the risk predictors we identified varied with those reported in several other studies because our endpoint (LAE) included only severe arrhythmias, whereas previous studies have often used composite endpoints including less severe arrhythmic events and antitachycardia pacing (e.g., the largest ARVC study by Groeneweg et al. [7]).

RESPONSE TO THERAPY. In our cohort, 40% of patients received sotalol, beta-blockers, or amiodarone; yet, none of these antiarrhythmic agents reduced LAE rates at follow-up in multivariable analysis. These findings concur with the observation that antiarrhythmic drugs in ARVC are palliative, and although they may attenuate symptoms, they do not reduce incidence of LAE or cardiovascular mortality (19). However, the possibility that drug treatment prevented a worsening of the arrhythmic profile as a consequence of the disease progression cannot be ruled out.

In our population, catheter ablation also was not associated with a reduction of LAE, although only 2 patients received a combined endocardial and epicardial ablation procedure, which has been associated with a favorable prognosis in patients with ARVC (27).

Facing the lack of survival benefit of antiarrhythmic therapy, it became particularly interesting to look at the role of ICDs in patients with ARVC. In our population, 47% of patients implanted for primary prevention of LAE received an appropriate shock that terminated the arrhythmia. These data support the conclusion that an ICD may be life-saving when appropriately used for primary prevention of SCD in high-risk patients with ARVC.

Despite the high rate of ICD-related complications we observed, it should be noted that we also included inappropriate shocks among the side effects of the ICD. Conversely, major complications requiring implant revision were observed in 6% of patients over 7 years of median observation.

STUDY LIMITATIONS. Our registry presented some limitations inherent to this kind of investigation. Specifically, despite all patients enrolled being referred to our center, they were also managed by their local cardiologist; therefore, our control of adherence to a pre-specified protocol for their clinical management was limited. Moreover, genetic screening was not performed in 100% of patients: we screened 94% of probands on plakophilin-2 and 82% of probands on desmoplakin, desmocollin-2, and desmoglein-2. Finally, parameters used for risk stratification were evaluated at the moment of first visit and, therefore, may have changed during 5.8 years of follow-up. We recognize that this assumption, despite being part of the methodology adopted in most prospective registries, might represent a limitation.

CONCLUSIONS

Our study contributes to defining the age-dependent profile of arrhythmic manifestations in ARVC, highlighting the onset of arrhythmic risk in teenage years. This information is critical to design screening programs aimed at the early detection of ARVC in patients involved in intense physical training, a factor associated with ARVC progression.

Our study also found that, although antiarrhythmic therapy did not prevent life-threatening arrhythmias, an ICD can be life-saving. ICD implantation, however, carries a high incidence of adverse events, mainly inappropriate shocks. A risk stratification scheme is therefore imperative to identify higher-risk patients who may benefit most from a defibrillator. In our study, the key factors associated with high risk of severe arrhythmias at follow-up were male sex, participation in strenuous exercise after the diagnosis, history of AF, syncope, and HT-MMVT. We recommend that in the presence of 1 or more of these clinical risk factors, an ICD should be considered.

ACKNOWLEDGMENTS The authors thank Antonio Curcio, MD, Matthew Francis, MS, and Katherine Underwood, MS, for their contributions. This work is dedicated to the authors' friend and colleague, Sean O'Rourke, MD.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Sudden death can be the initial clinical manifestation of ARVC. Aside from male sex, a history of syncope, of hemodynamically-tolerated sustained monomorphic VT, or of AF, and participation in strenuous exercise after the diagnosis increased the risk of life-threatening arrhythmias in patients with this disorder.

TRANSLATIONAL OUTLOOK: Future investigations should be directed at defining more specific risk factors for arrhythmic death in patients with ARVC.

JACC VOL. 68, NO. 23, 2016
DECEMBER 13, 2016:2540–50

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KEY WORDS athletes, genetics, implantable cardioverter-defibrillator, sudden cardiac death, ventricular tachycardia

APPENDIX For an expanded Methods section as well as supplemental figures and tables, please see the online version of this article.