Risk Stratification in Arrhythmogenic RV Cardiomyopathy Dysplasia Without an ICD

Introduction

Arrhythmogenic cardiomyopathy (AC), formerly known as arrhythmogenic right ventricular cardiomyopathy (ARVC) or arrhythmogenic right ventricular dysplasia (ARVD), is an inherited condition in which fibro-fatty replacement of the myocardium may lead to ventricular arrhythmias (VA), and sudden cardiac death (SCD) and ventricular dysfunction, .[1,2] The identification of causal genetic variants in desmosomal genes, inherited in an autosomal dominant manner with incomplete penetrance and variable expressivity, has led to ARVC being considered a "disease of the desmosome."[3] Disease expression is highly variable even among members of the same family with the same genetic variant, making clinical detection and screening arduous. Because electrical abnormalities can precede structural abnormalities with SCD as the first tragic and lethal manifestation, especially in young adults with many potential years of life lost, optimizing screening strategies is of paramount importance.

Treatment options for managing VA and SCD risk in ARVC include antiarrhythmic drugs, implantable cardioverter defibrillators (ICDs), catheter ablation, and sympathectomy. Decisions should be individualized with risks and benefits evaluated.

The only evidence-based therapies for SCD mitigation are ICDs, and implanting an ICD for secondary prevention in patients with resuscitated cardiac arrest or hemodynamically unstable ventricular tachycardia (VT) is usually straightforward. However, for primary prevention, the clinician is faced with a difficult task. Recommending an ICD to the correct patient and preventing death provides great benefit with minimal risk. Implanting an ICD in a patient who is low risk and has no events but may get complications imparts higher risk but lesser benefit. Denying an ICD to a patient who then goes on to have a sentinel event is the worst-case scenario; this has historically led to an overly cautious approach. Finally, patients who are *compos mentis* may accept

the risk of SCD with a full understanding but choose not to have an ICD and seek alternatives. In this article, we discuss options for managing VA and SCD risk in patients with ARVC *without* an ICD.

Diagnosing ARVC: The diagnosis of ARVC should be highly suspected when there are overt structural and ECG changes, particularly in more advanced disease. There are four recognized phases of ARVC:

The concealed phase	**Subtle structural changes within the RV, Usually no symptoms, May have minor VT. High risk of SCD. The concealed phase precedes the development of ECG, structural, and histological changes but may be associated with a high arrhythmia burden and risk of SCD. During this phase, patients can present with a variety of symptoms, including intermittent chest pain and myocardial enzyme release, which may be diagnosed as myocarditis. Thus, diagnosing ARVC is more challenging when early disease has few consistent features and when possible phenocopies are in the differential.**
Overt phase: An overt electric disorder	Noticeable structural/functional changes within the RV, Symptoms ventricular dysrhythmias, presyncope, syncope, palpitations
Right ventricular (RV) failure	RV dilates and weakens, RV failure symptoms: edema of legs or ankles, abdominal distension, dyspepsia, anorexia
The advanced phase, severe diffuse biventricular pump failure that can resemble dilated cardiomyopathy	LV dilates and weakens, HF Symptoms: dyspnea on exertion, orthopnea, breathlessness.

Source: Cardiomyopathy Association, http://www.cardiomyopathy.org

At present, there are no gold-standard tests or pathognomonic criteria to make a definitive diagnosis of ARVC. The 2010 Task Force Criteria facilitate diagnosis with an emphasis on major (each scores 2 points) and minor (each scores 1 point) criteria that include 6 domains:

1. Structural abnormalities
2. Histopathological findings
3. Repolarization abnormalities
4. Depolarization abnormalities
5. Arrhythmia
6. Family history

A diagnosis of *definite* ARVC requires 4 points in any of the following combinations: 2 major criteria, 1 major and 2 minor criteria, or 4 minor criteria. The diagnosis is *borderline* if there are 3 points (1 major criterion and 1 minor criterion or 3 minor criteria), and *possible* if there are 2 points (1 major criterion or 2 minor criteria). Although these criteria are more sensitive, they are difficult to robustly apply when used for screening family members and asymptomatic variant carriers and eliminating other possible diagnoses like myocarditis, sarcoidosis, dilated cardiomyopathy, Brugada syndrome, Uhl anomaly, Ebstein's anomaly, a left-to-right shunt, and pulmonary hypertension.

Once a diagnosis of ARVC is made, key management decisions include the following:

1. Risk stratification for the occurrence of VA and SCD
2. Preventing disease progression
3. Minimizing arrhythmic burden
4. Cascade screening of family member

A shared-decision making model has to incorporate estimates of risk and patient preferences and values.

We discuss our approach to management below.

Risk Stratification for VA and SCD

The risk of VA and SCD in ARVC is based on small, single-center observational studies and some multicenter studies. No prospective randomized studies exist and are unlikely to be conducted due to feasibility. The incidence of ARVC in the United States is estimated to be between 0.01 and 0.1%, but it is likely to be higher because it is underdiagnosed.[4] In Italy, ARVC is the leading cause of sudden death in athletes,[5] and those under 40 years of age have an estimated incidence of 0.04%. Nevertheless, it is a rare disease with broad phenotypic heterogeneity with no uniform standards for phenotyping. Currently, we lack the tools and knowledge to forecast stable VA from SCD events, making randomized studies non-feasible and ethically unjustifiable. Thus, risk prediction is based on observational data and expert consensus.

What Do the Experts Say?

The 2015 International Task Force Consensus Statement on risk stratification recommends ICD implantation for all high-risk cases, which includes secondary prevention for aborted SCD and sustained VA and primary prevention for cases with severe dysfunction of either or both ventricles. Low-risk groups are those with no risk factors and "healthy carriers" (with a negative genetic test for known pathogenic variants).[6] Those in the intermediate category have a Class IIa recommendation for risk stratification based on ≥1 major risk factors for syncope and electrical instability with nonsustained VT (NSVT) or moderate dysfunction of the LV RV, or both ventricles. The presence of ≥1 minor risk factor (compound heterozygotes, digenic carriers, electroanatomic scar on RV endocardial voltage mapping per 5% increment, fragmented ECGs, T-wave inversion in inferior leads, T-wave inversion in 2 out of 3 inferior leads, T-wave inversion in ≥3 precordial leads, QRS fragmentation and precordial QRS amplitude ratio <0.48) is given a Class IIb recommendation for consideration of ICD implantation. The role of electrophysiology studies (EPS),

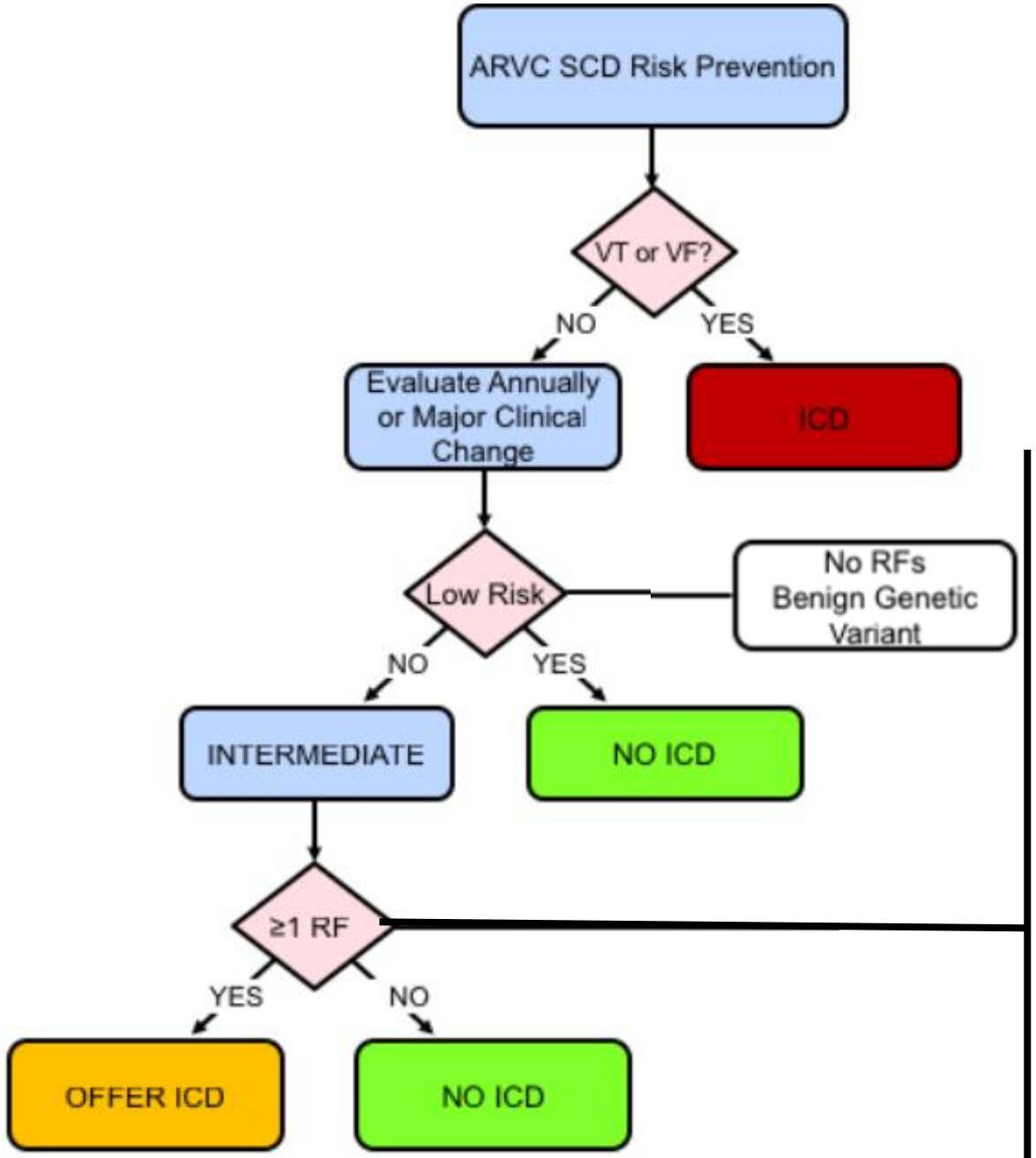
programmed ventricular stimulation (PVS), and endocardial voltage mapping is also discussed in the evaluation with a Class IIa recommendation for EPS and Class IIb recommendation for both PVS and voltage mapping.

General approach to primary prevention is to consider the following variables:

1. Age
2. Male sex
3. Presence of unexplained syncope that may reflect an episode of VA
4. Electrical instability of NSVT or a high premature ventricular contraction (PVC) frequency on Holter monitoring(ECG)
5. Pathogenic genetic variants
6. Vigorous or sustained exercise
7. Evidence of abnormal substrate with slow conduction at invasive electroanatomic mapping with presence of fragmented/split/late electrograms, particularly in the setting of a large scar burden
8. Inducibility of VA with PVS
9. Tissue characterization by cardiac magnetic resonance (CMR)

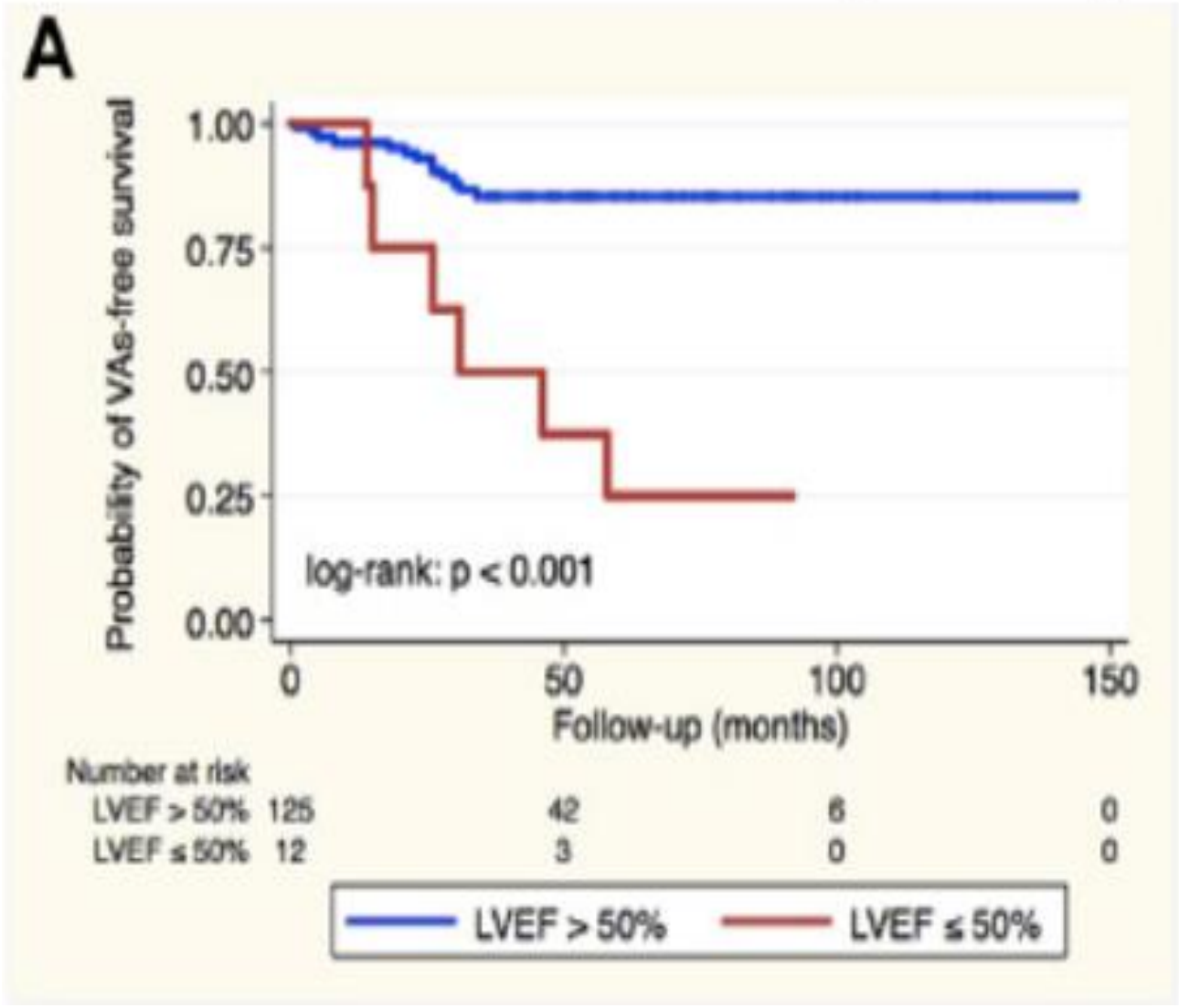
These variables are discussed below with relevant supporting literature (Figure 1). The important caveats to interpretation are that most data are from retrospective studies, inherent to studying rare diseases, VA, and SCD events. Most studies are natural history or secondary prevention observational studies,[7-12] but a few prospective primary prevention observational studies exist.[13,14] One of these was recently published, evaluating clinical risk factors associated with arrhythmic events and SCD in 137 consecutive patients with a diagnosis of ARVC without ICDs enrolled over a 10-year period.[14] Each individual underwent an EPS; ICD implantation resulted in censoring at the date of implantation, and only the period before VA occurrence was analyzed. After a mean follow-up of 42 ± 31 months, 19 patients (13.9%) experienced an episode of sustained VA, and 5 patients (3.6%) experienced SCD or aborted SCD. Asymptomatic patients experienced no events, but LVEF≤50% ($p = 0.024$), a positive EPS ($p = 0.017$), and physical activity >6 h/week ($p = 0.025$) were independently associated with occurrence of VA (Figure 2). Aborted and full SCD only occurred in male probands with a definite diagnosis and syncope. A positive EPS was sensitive at predicting VA but did not predict SCD.

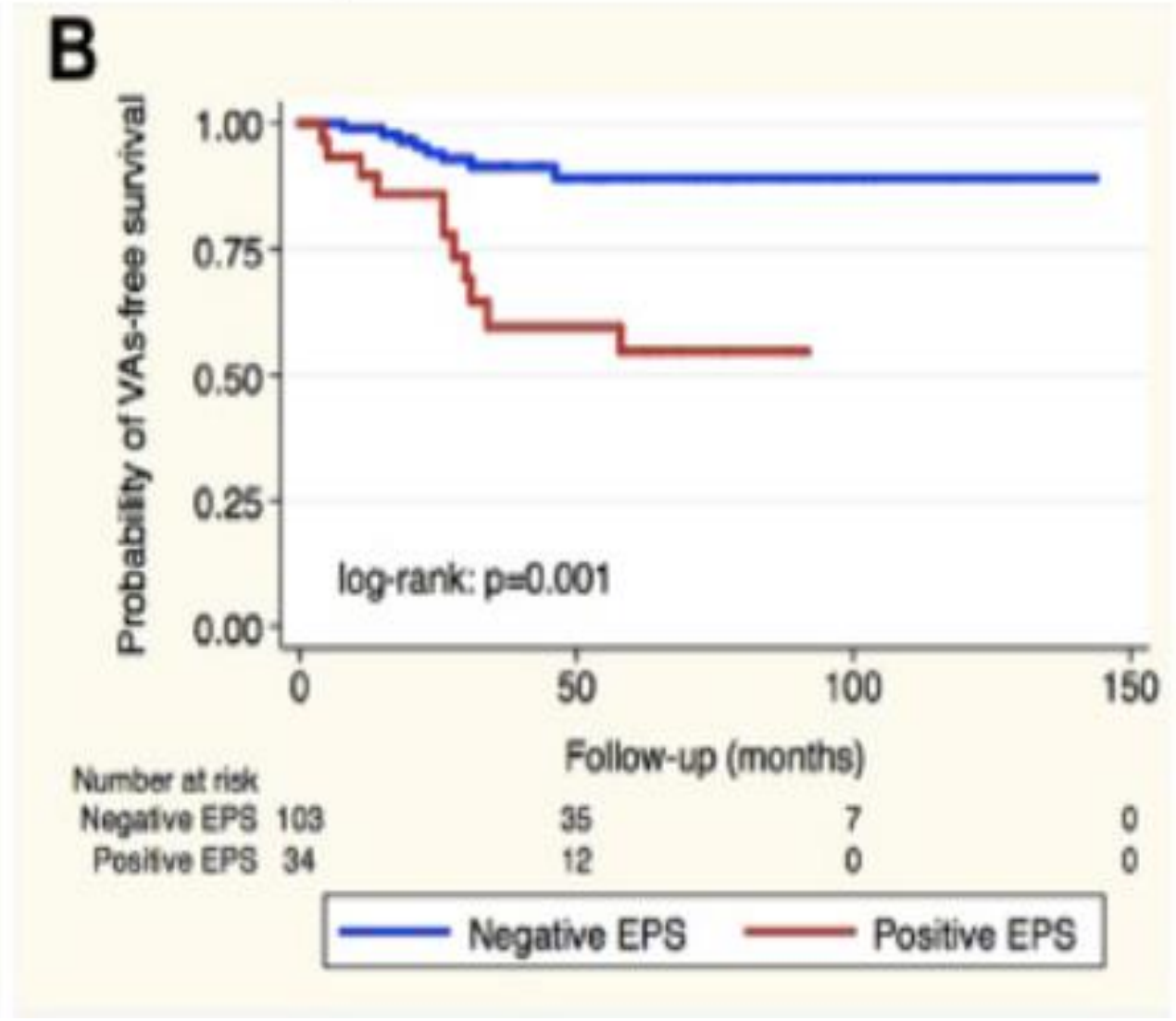
Figure 1: Flow Chart for ICD Implantation



Age
Male sex
Presence of unexplained syncope which may reflect ar
episode of VA;
Electrical instability of NSVT or high PVC frequency
Pathogenic genetic variants;
Vigorous or sustained exercise;
Evidence of abnormal substrate with slow conduction at
invasive electroanatomic mapping
Presence of fragmented/split/late electrograms,
particularly in the setting of a large scar burden;
Inducibility of VA with PVS
LGE on CMR

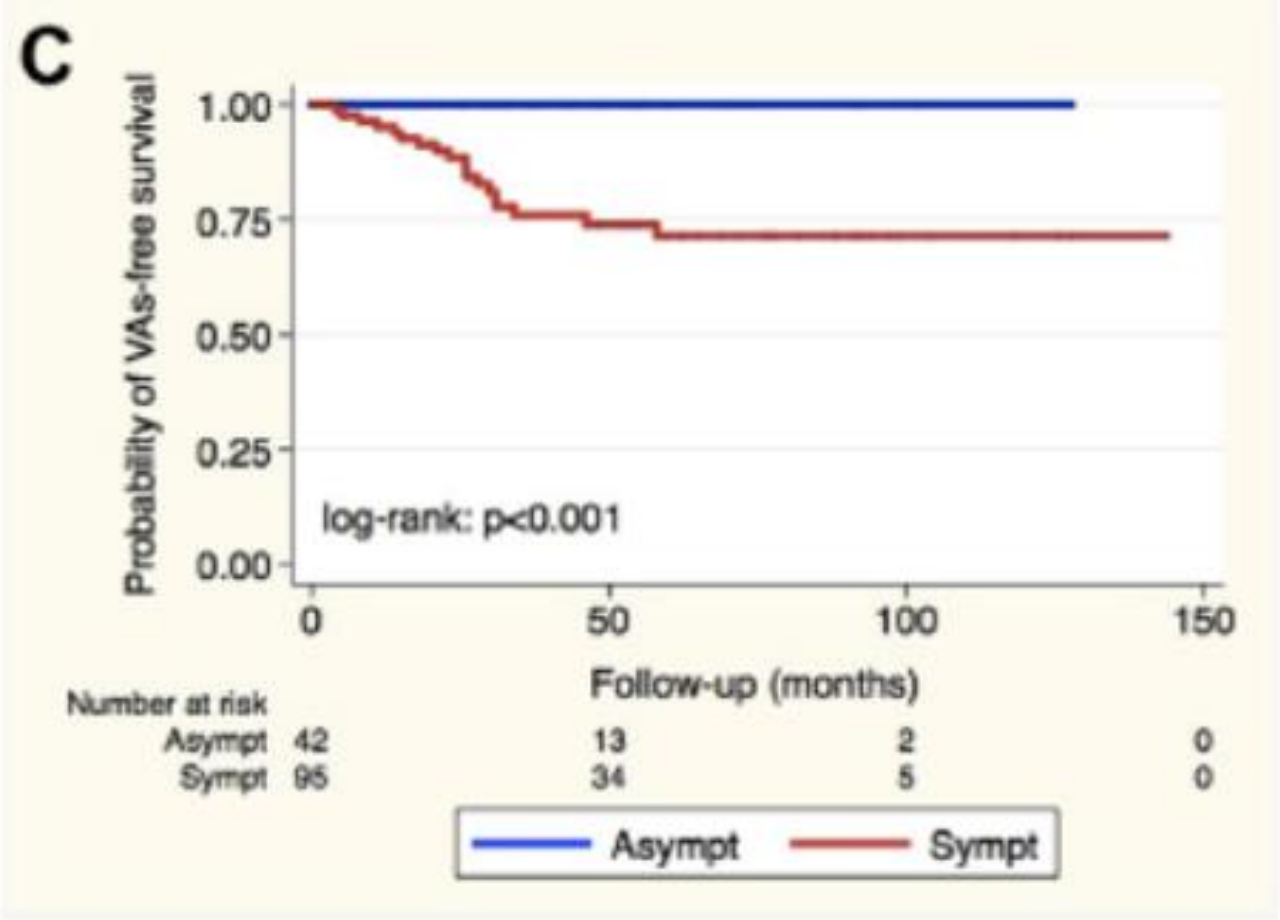
Figure 2: Kaplan-Meier Analysis of Cumulative Survival From all VA

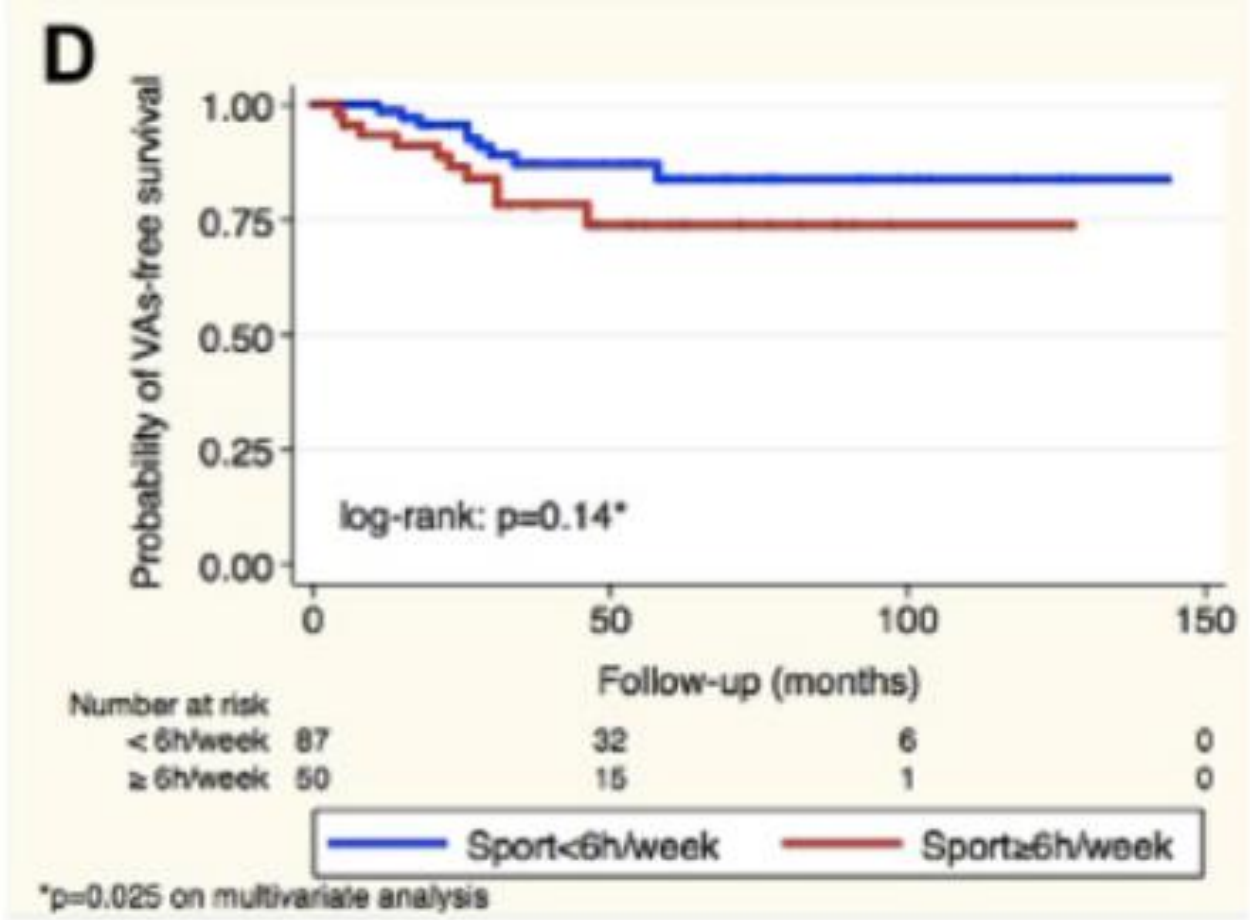




A) Primary endpoint (defined as syncope, spontaneous sustained VT, or SCD or aborted cardiac arrest) according to LVEF.

B) EPS results (EPS was considered positive when sustained VT or ventricular fibrillation was induced.





(**C**) Presence of symptoms (defined as palpitations, syncope, pre-syncope, or congestive heart failure).

(**D**) Physical activity. *Reproduced with permission from Maupain et al.*[14]

1. *Age*: A diagnosis of ARVC before adolescence and after the age of 60 years is rare, with the usual age of presentation in early adulthood. In the largest study of ARVC patients (n = 439) from an American and a Dutch center, the mean age of presentation in index cases was 36 ± 14 years, with 48 (11%) presenting with cardiac arrest.[7] Of these 48 patients, 25 were resuscitated, and 23 died with diagnosis at post-mortem. Median age at cardiac arrest was 25 years. Of the index cases, 220 (50.1%) presented with sustained VA, and an ICD was implanted in 212 (87%) of 245 cases with a history of sustained VA or aborted SCD. Of the index cases without VA or aborted SCD, 139 (81%) received an ICD, leaving 65 index cases without an ICD. Over the median study follow-up period of 5 years, 31 patients (48%) experienced a sustained VA. Arrhythmic events tended to occur in younger patients with pathogenic variants in known ARVC genes. These findings have been observed in other studies in which ICDs were implanted in younger patients for secondary prevention, as well as higher frequency of VA in primary prevention recipients.[8,15]

2. *Male Sex :* In the largest study reporting outcomes of ICD therapy, male sex was a predictor of any ICD therapy (hazard ratio [HR] 1.62; 95% confidence interval [CI], 1.20-2.19; p = 0.00).[16] In the aforementioned prospective primary prevention study, male sex was exclusively a risk factor for SCD or aborted SCD.[14] Similarly, a meta-analysis of 18 studies, male sex had a pooled HR of 1.83 (95% CI, 1.41-2.37; p = 0.001).[17] Although the majority of ARVC cases are autosomal dominant and monogenic (i.e., not compound heterozygotes or digenic), the expected frequency of sex distribution would be 1:1. However, most studies, irrespective of VA or SCD have a male preponderance, which may genuinely reflect higher prevalence or severity of disease amongst males, sex-based differences, or lifestyle differences such as male propensity for more frequent and intense exercise. Given the higher frequency of male sex, this may be a confounder reflecting higher observed risk of VA and SCD in male patients. These may also reflect that female patients tolerate symptoms and present at a later stage than male patients.

3. ***Presence of Unexplained Syncope That May Reflect an Episode of VA:*** Unexplained syncope (loss of consciousness that occurs in the absence of documented VA or reflex-mediated changes and remains unexplained after detailed clinical evaluation to exclude other cardiac or extracardiac causes) has been associated with an increased arrhythmic risk in some but not all studies.[17] Clues that unexplained syncope may be arrhythmogenic include severe injuries, particularly to the face when the person may not have had sufficient warning to break a fall. The presence of rapid palpitations and associated symptoms such as diaphoresis, dyspnea, and pre-syncope are also suggestive of an arrhythmic cause.

4. ***Electrical Instability of NSVT or a High PVC Frequency on Ambulatory ECG*** the presence of >500 PVCs in 24 hours is a minor criterion for the diagnosis of ARVC. NSVT with a left bundle branch block and superiorly directed morphology is considered a major criterion, and other NSVTs are considered minor criteria. Multiple studies have shown these PVCs and NSVTs to be risk factors for VA and SCD. In a retrospective study of 84 recipients of an ICD for primary prevention, inducibility at EPS ($p = 0.005$), presence of NSVT ($p < 0.001$), and Holter PVC count >1,000/24 hours ($p = 0.024$) were identified as significant predictors of appropriate ICD therapy.18 The PVC frequency or burden was also associated with increased arrhythmic risk.

5. ***Pathogenic Genetic Variants:*** Genetic testing varies depending on the technology used, and at present there are 11 known associated genes that are broadly divided into desmosomal and non-desmosomal groups.[19] Desmosomal genes include desmoplakin, desmocollin 2, desmoglein 2, plakophilin 2, α-catenin, Titin, plakoglobin, and cadherin-2. Non-desmosomal genes include ryanodine-receptor 2, transforming growth factor beta-3 preprotein, *LMNA* (encodes Lamin A-C, which stabilizes cells), and transmembrane protein 43 (*TMEM43*) In addition, two loci identified and termed *ARVD3* (chromosome 14q12-q22) and *ARVD6* (chromosome 10p14-p12) have not at present had the genes identified. The presence of two pathogenic variants in a single gene (compound heterozygotes) and carriers of multiple gene variants are generally recognized as conferring higher risk for more advanced disease, including VA and SCD. Certain genes and variants alone, such as missense mutations

in *TMEM43 (p.S358L)* have been shown to be highly penetrant and lethal.[20] However, many variants are private to family members or specific to regions, probably representing founder effects.

The other important consideration is that some family members may carry the known or likely pathogenic variant but display no phenotypic features and thus are termed *asymptomatic variant carriers*. A prospective study of desmosomal pathogenic variant carriers followed-up for a mean 8.5 years reported major arrhythmic events that occurred in carriers who were classified as *definite* by Task Force Criteria, and Task Force Criteria-negative individuals had benign course.[21] There was one exception of a 15-year-old individual who died suddenly during sleep 2 years after being identified as genotype-positive. This individual had a normal ECG and echocardiogram but had epicardial scar in the inferolateral wall of the LV. Involvement of this area is frequently seen in myocarditis, and it is plausible that a viral or other trigger in a desmosomal mutation carrier increased the likelihood of developing myocarditis, resulting in fatal VA. This case underscores the importance of more frequent screening and the use of CMR.

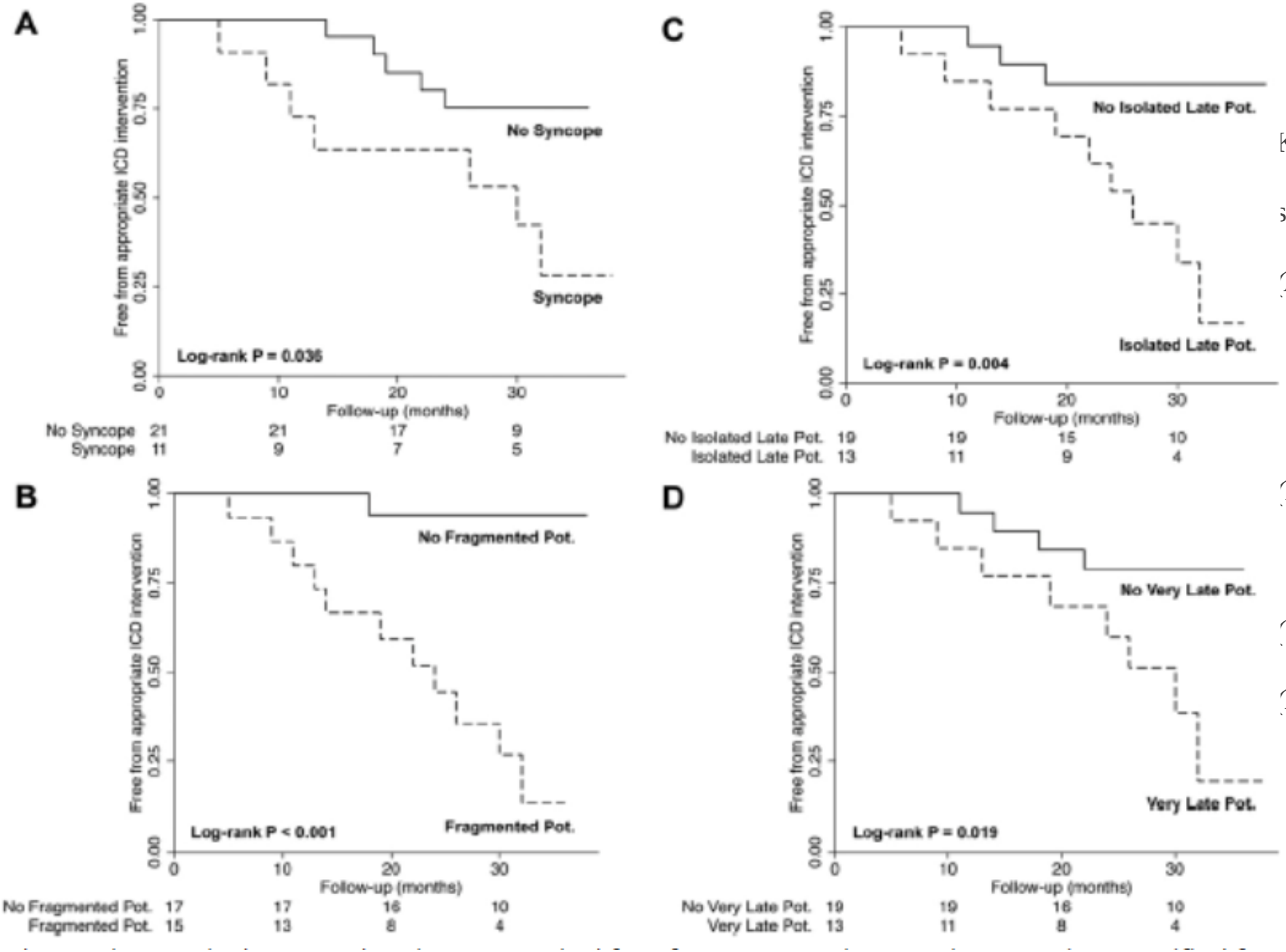
6. *Vigorous or Sustained Exercise:* Exercise restriction can decrease disease progression as well as the occurrence of VA.[22-27] This has not been uniformly reported in studies assessing VA and SCD risk and has not been quantified. In general, sustained or high-intensity exercise is associated with more advanced and earlier disease, including early age of onset of VA, structural dysfunction, heart failure, and need for transplantation.

The Johns Hopkins Hospital's practice is to restrict exercise in all cases of definite ARVC, irrespective of genotype,[24] whereas other experts restrict exercise in only those with desmosomal variants. Light exercise is recommended in asymptomatic variant carriers. Our experience and recommendations are to restrict sudden-onset, high-intensity exercise and endurance exercise in those with desmosomal variants but to encourage low-intensity exercise in borderline cases and asymptomatic variant carriers because of the general benefits of physical activity. An important distinction exists between competitive athletics and recreational exercise, and the two are often confused. The most recent scientific statement

from the American Heart Association and American College of Cardiology recommends that all cases of definite and borderline ARVC should avoid all competitive sports with the exception of low-intensity class 1A sports (billiards, bowling, cricket, curling, golf, and riflery).[28] Light exercise, as recommended by the American Heart Association minimal exercise requirements, is likely safe and brings other benefits that outweigh the potential harm.[29]

7. *Invasive Electroanatomic Mapping With Evidence of Slow Conduction and Scar Burden*

In a prospective study of 32 patients with ARVC and a primary prevention ICD (i.e., no prior history of cardiac arrest or sustained VA), high-density RV electroanatomical mapping was performed to test the association of fragmented electrograms with scar and arrhythmic events.[13] Over a mean follow-up of 25 ± 7 months, 12 patients (38%) received appropriate ICD shocks for sustained VA. Patients with shocks versus without shocks were similar clinically by late gadolinium enhancement on CMR and distribution and extent of electroanatomical scar (38 ± 25 cm^2 vs. 33 ± 20 cm^2; p = 0.51), with the exception of a higher frequency of syncope in the group with shocks (p = 0.053). However, patients with appropriate shocks had a higher prevalence of fragmented electrograms (92% vs. 20%; p = 0.001), of isolated late potentials (75% vs. 20%; p = 0.004), and of very late potentials (67% vs. 25%; p = 0.030). Fragmented electrograms were also independently associated with arrhythmic events at follow-up (HR 21; 95% CI, 1.79-251.83) (Figure 3).



Kaplan-Meier survival curves showing

(A) survival free from appropriate ICD intervention stratified for history of syncope

(B) presence of fragmented potentials,

(C) isolate late potentials, or

(D) (very late potentials. Reproduced with permission from Santangeli et al.[13]

The presence of a large burden of scar assessed by electroanatomical voltage mapping has also been associated with the risk of VA and SCD. In a study of 69 patients with ARVC (47 males, median age 35, interquartile range [IQR] 28-45 years) who underwent bipolar and unipolar voltage maps for primary and secondary prevention, the presence of an abnormal bipolar voltage area (<1.5 mV for each 5% area) was associated with increased risk of appropriate ICD shocks (HR 1.7 per 5%; 95% CI, 1.5-2.0; $p < 0.001$).[30] This remained a predictor whether or not RV dysfunction was present, and a normal bipolar voltage map was associated with an uneventful course over a median follow-up period of 41 months (IQR 28-56). In our experience, CMR may not demonstrate fibrosis with late gadolinium enhancement with equivocal demonstration of fatty metaplasia. Even with mild RV dysfunction, bipolar and unipolar voltage maps can identify abnormal areas of myocardium, thus guiding phenotyping. The presence of a large area of scar and inducibility of VA from this area would favor ICD implantation.

8. ***Inducibility of VA With PVS:*** Multiple studies have reported that sustained VA during PVS are prognostic markers of future events,[16,18,31-33] and one study has reported that they are not predictive.[34] Our experience supports the role of EPS at index evaluation and also for distinguishing phenocopies of outflow tract tachycardia and cardiac sarcoidosis. The identification of monomorphic outflow tract tachycardias makes a diagnosis of ARVC less likely and also has a more favorable prognosis in terms of SCD risk as well as being curable by catheter ablation with minimal risk. A meta-analysis found VA induced at EPS was predictive of VA risk in borderline cases (HR 3.24; 95% CI, 1.95-5.39; $p < 0 .001$) but was not useful in those with a definite diagnosis of ARVC (HR 1.02; 95% CI, 0.32-2.64; $p = 0.968$).[17]

9. ***Tissue Characterization by CMR:*** CMR imaging is an invaluable tool in the diagnosis and evaluation of ARVC, particularly to distinguish phenocopies, provide validated and reliable chamber volumes and functional quantification, exclude the presence of thrombus, and use for tissue characterization.[35] Although the presence and absence of fatty infiltration can be identified, it is limited in cases when this is microscopic and can occur in other cardiomyopathies. Strain by CMR is emerging as a useful tool but has not been validated, and its use is limited to research settings.

***More Recent Data*:** In a prospective study of 117 probands and genotype-positive family members (29% probands, 50% female) with a median 4.2 years (IQR 2.4-7.4), 18 (15%) experienced life-threatening VA.[36] The strongest predictors included a history of high-intensity exercise (adjusted HR 4.7; 95% CI, 1.2-17.5; p = 0.02), T-wave inversions (in ≥3 leads; HR 4.7; 95% CI, 1.6-13.9; p = 0.005), and greater LV mechanical dispersion by strain analysis (HR 1.4; 95% CI, 1.2-1.6 by 10 ms increments; p < 0.001). Individuals without any of these 3 risk factors had minimal risk, whereas the presence of ≥2 risk factors increased the risk.

Role of Catheter Ablation and Anti-Arrhythmic Drugs: Although we make the recommendation for an ICD for secondary prevention and high-risk primary prevention, certain patients elect not to have an ICD for a number of reasons:

1. Recognizing they have stable VA
2. Avoiding inappropriate ICD shocks
3. Attempting management with alternatives first
4. Restrictions to lifestyle
5. Potential long-term complications

In these patients who make an informed choice not to have an ICD, alternatives of catheter ablation and anti-arrhythmic drugs can be offered while making it clear that they do not have the same robustness of supporting evidence for SCD prevention. One of the key components of successful catheter ablation is eliminating areas of slow electrical conduction within the abnormal substrate that can be responsible for malignant reentrant VA. Given the typical epicardial to endocardial distribution of the substrate, a combined endocardial and epicardial ablation strategy is often needed. In a prospective study of 49 patients, a combinedendocardial-epicardial approach (n = 26) versus an endocardial-only approach (n = 23) was associated with a higher freedom from VA or ICD therapies (84.6% [22/26] vs. 52.2% [12/23]) after a follow-up period of at least 3 years (p =

0.029).[37] Although all patients had an ICD for secondary prevention, the aims of the study were to determine predictors of arrhythmia-free success. These data are relevant to patients who develop VA and decline an ICD. Recurrent VT is largely thought to be due to advanced disease progression resulting in abnormal areas of scar formation, although there is no conclusive evidence supporting this concept. In a retrospective study of ARVC patients who underwent repeat catheter ablation for VT, this concept was challenged because only 18% of patients had demonstrable scar progression with serial bipolar voltage mapping.[38] However, RV dilation occurred in the majority, and it remains unclear whether RV dilatation in the absence of a demonstrated increase in scar size should be viewed as true disease progression (i.e., progressive fibro-fatty replacement of RV myocardium) versus adverse remodeling. These data also support the concept that a complete endocardial-epicardial substrate ablation may result in lasting VT control in these patients. In an international multicenter VT study of 32 patients with ARVC who underwent catheter ablation for VT and chose not to have an ICD (due to refusal or financial costs), there were no mortality events over a median follow-up of 46 months (range 26-65).[39] Recurrence of VT occurred in only 19% of patients without any injury and in 75% without the need for an anti-arrhythmic drug. Although these data are not strong enough to support no ICD, they are indicative of good outcomes using catheter ablation as a first-line therapy in patients who refuse an ICD. Furthermore, they provide additional evidence supporting a strong role of catheter ablation also in patients with an ICD in order to markedly reduce the need for appropriate ICD therapies. Sotalol and amiodarone are the most used anti-arrhythmic to protect against VT episodes and improve symptoms, but they have limited efficacy. Sotalol is more useful for the acute prevention of VT or ventricular fibrillation induction, and amiodarone may be more efficacious in preventing VA.[40] When prescribing amiodarone to prevent VA, particularly in younger patients, physicians should be mindful of the potentially serious adverse events (including risk for life-threatening end-organ toxicity) mostly associated to the long-term exposure.[41,42] More recent evidence supports a role for flecainide to control VA in ARVC, although additional large studies are needed to establish the efficacy and safety profile of flecainide in this setting.

Summary

Risk-prediction for VA and SCD events should occur at index evaluation, at *every* follow-up visit, and when there is a major change in clinical status given the dynamic nature of ARVC. Our approach to comprehensive phenotyping at index evaluation includes detailed clinical history, family history, 12-lead ECG, signal-averaged ECG, minimum 24-hour Holter monitoring annually, targeted panel genetic testing, transthoracic echocardiography, CMR, 18F-fludeoxyglucose positron emission tomography-computed tomography, EPS with PVS, unipolar and bipolar voltage maps, and identifying abnormal fractionated electrograms and late potentials. Occasionally, for equivocal cases, a voltage- and/or magnetic resonance imaging-guided biopsy is performed. We categorize risk into low, intermediate, and high risk and, using a shared decision-making approach, offer an ICD to those at high risk and observe those at low risk. For intermediate cases, we determine patient preference and pursue multidisciplinary management with specialists in inherited cardiovascular disease, heart failure, and electrophysiology. Catheter ablation and anti-arrhythmic drugs are offered to reduce the burden of VA and to those isolated individuals who decline ICD implantation.

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ARVC Risk Calculator

Please read the disclaimer in next slide before use and interpretation of the calculated result.

Age at diagnosis

Enter the age at which the patient fulfilled ARVC diagnosis as per 2010 modified Task Force Criteria (Marcus et al. 2010)

Sex

Male Female

Cardiac syncope (<6 months)

Yes No

Specify if the patient experienced syncope suspected to be caused by cardiac arrhythmia in the 6 months prior to diagnosis.

Number of inverted T-waves

0 to 6

Specify the total number of inverted T-waves in precordial and inferior leads on standard 12-lead ECG.

Maximum 24 hours PVC count

Enter the maximum number of PVCs measured in 24 hours by ECG/Holter monitoring.

History of non-sustained VT

Yes No

Specified as a recorded ventricular tachycardia (>100bpm) ending spontaneously within 30 seconds.

Right ventricular ejection fraction (%)

50

As measured by cardiac MRI.

Risk of sustained ventricular arrhythmia

Disclaimer

This website hosted by the Netherlands Heart Institute is for information and training purpose only, The Netherlands Heart Institute nor the individual researchers involved in this project carry responsibility for medical decisions made with the information provided by this website.

The ARVC risk calculator is based on clinical data of patients fulfilling ARVC diagnosis as per modified Task Force Criteria (TFC) [1] from 14 academic centers worldwide [2]. It estimates the risk of sustained ventricular tachycardia in newly diagnosed patients who fulfill 2010 TFC for definite diagnosis of ARVC but have not experienced prior sustained ventricular arrhythmias. The aim of the individualized predictions is to aid patients and clinicians in their decision to implant an implantable cardioverter-defibrillator for primary prevention of sudden cardiac arrest.

Our prediction model is currently not part of any clinical guideline and should not be used to replace the standard of care. Please take into consideration that this model has not been validated in external cohorts. The estimated risk from our calculator is based on the population of patients included our original study and may not provide an accurate estimation in the specific circumstances of patients outside this cohort. **The use and interpretation of the results provided by the calculator are at the responsibility of the user.**

This calculator should **not be used in patients with prior sustained ventricular arrhythmia or sudden cardiac arrest**, as these were not included in the study cohort.

The predictions this calculator provides are based on clinical characteristics of patients at time of their diagnosis (within a time frame of ca. 1 year), therefore its application is meant for **newly diagnosed** patients (according to 2010 TFC). Pending further research, interpretation of predictions by entering characteristics during follow-up is discouraged.

Caution should be exercised when interpreting the prediction for patients **<14 years of age**, as the cohort this prediction model was based on only contained 2% pediatric patients <14 years.

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The Revised Task Force Criteria for ARVD / ARVC(1)

Ⅰ. Global or regional dysfunction and structural alterations∗ Major/Minor

Major By 2D echo:	**Minor By 2D echo**
Regional RV akinesia, dyskinesia, or aneurysm and 1 of the following (end diastole): PLAX RVOT ≥32 mm (corrected for body size [PLAX/BSA] ≥19 mm/m2) PSAX RVOT ≥36 mm (corrected for body size [PSAX/BSA] ≥21 mm/m2) *or* fractional area change ≤33%	Regional RV akinesia or dyskinesia *and* 1 of the following (end diastole): PLAX RVOT ≥29 to <32 mm (corrected for body size [PLAX/BSA] ≥16 to <19 mm/m2) PSAX RVOT ≥32 to <36 mm (corrected for body size [PSAX/BSA] ≥18 to <21 mm/m2) *or* fractional area change >33% to ≤40%
By MRI:	**By MRI**
Regional RV akinesia or dyskinesia or dyssynchronous RV contraction *and* 1 of the following: Ratio of RV end-diastolic volume to BSA ≥110 mL/m2 (male) or ≥100 mL/m2 (female) *or* RV ejection fraction ≤40%	Regional RV akinesia or dyskinesia or dyssynchronous RV contraction *and* 1 of the following: Ratio of RV end-diastolic volume to BSA ≥100 to <110 mL/m2 (male) or ≥90 to <100 mL/m2 (female) *or* RV ejection fraction >40% to ≤45%
By RV angiography:	
Regional RV akinesia, dyskinesia, or aneurysm	

II. Tissue characterization of wall

Major	Minor
Residual myocytes <60% by morphometric analysis (or <50% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy	Residual myocytes 60% to 75% by morphometric analysis (or 50% to 65% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy

III. Repolarization abnormalities

Major	Minor
Inverted T waves in right precordial leads (V1, V2, and V3) or beyond in individuals >14 years of age (in the absence of complete RBB QRS ≥120 ms)	Inverted T waves in leads V_1 and V_2 in individuals >14 years of age (in the absence of complete right bundle-branch block) or in V4, V5, or V6 Inverted T waves in leads V_1, V_2, V_3, and V_4 in individuals >14 years of age in the presence of complete RBBB

IV. Depolarization/conduction abnormalities

Major	Minor
Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V_1 to V_3)	•Late potentials by SAECG in ≥1 of 3 parameters in the absence of a QRS duration of ≥110 ms on the standard ECG
	•Filtered QRS duration (fQRS) ≥114 ms

	Duration of terminal QRS <40 μV (low-amplitude signal duration) ≥38 ms
	Root-mean-square voltage of terminal 40 ms ≤20 μV
	Terminal activation duration of QRS ≥55 ms measured from the nadir of the S wave to the end of the QRS, including R′, in V_1, V_2, or V_3, in the absence of complete right bundle-branch block

V) Ventricular Arrhythmias

Major	**Minor**
Nonsustained or sustained ventricular tachycardia of left bundle-branch morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL)	•Non-SVT or S-VT of RV outflow configuration, LBBB morphology with inferior axis (positive QRS in leads II, III, and aVF and negative in lead aVL) or of unknown axis • >500 PVCs per 24 hours (Holter)

VI. Family history

Major	**Minor**
•ARVC/D confirmed in a first-degree relative who meets current Task Force criteria	•History of ARVC/D in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current Task Force criteria
•ARVC/D confirmed pathologically at autopsy or surgery in a first-degree relative	•Premature sudden death (<35 years of age) due to suspected ARVC/D in a first-degree relative

•Identification of a pathogenic mutation† categorized as associated or probably associated with ARVC/D in the patient under evaluation	ARVC/D confirmed pathologically or by current Task Force Criteria in second-degree relative

PLAX indicates parasternal long-axis view; RVOT, RV outflow tract; BSA, body surface area; PSAX, parasternal short-axis view; aVF, augmented voltage unipolar left foot lead; and aVL, augmented voltage unipolar left arm lead.

Diagnostic terminology for original criteria: This diagnosis is fulfilled by the presence of 2 major, or 1 major plus 2 minor criteria or 4 minor criteria from different groups. Diagnostic terminology for revised criteria: definite diagnosis: 2 major or 1 major and 2 minor criteria or 4 minor from different categories; borderline: 1 major and 1 minor or 3 minor criteria from different categories; possible: 1 major or 2 minor criteria from different categories.

∗ Hypokinesis is not included in this or subsequent definitions of RV regional wall motion abnormalities for the proposed modified criteria.

† A pathogenic mutation is a DNA alteration associated with ARVC/D that alters or is expected to alter the encoded protein, is unobserved or rare in a large non–ARVC/D control population, and either alters or is predicted to alter the structure or function of the protein or has demonstrated linkage to the disease phenotype in a conclusive pedigree. E.g.: in TMEM43, DSP, PKP2, DSG2, DSC2, JUP.

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