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REVIEW

Management of arrhythmogenic right ventricular cardiomyopathy

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ABSTRACT

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetically determined heart muscle disorder, predisposing to sudden cardiac death (SCD), particularly in young patients and athletes. Pathological features include loss of myocytes and fibrofatty replacement of right ventricular myocardium; a biventricular involvement is often observed. The diagnosis of ARVC (prevalence 1:5.000 in the general population) does not rely on a single gold standard test but is achieved using a scoring system, proposed in 2010 by an International Task Force, which encompasses familial and genetic factors, ECG abnormalities, arrhythmias, and structural/functional ventricular alterations. The main goal of treatment is the prevention of SCD. Implantable cardioverter defibrillator (ICD) is the only proven "lifesaving" therapy; however, it is associated with a significant morbidity due to device-related complications and inappropriate ICD interventions. Other treatment options such as life style changes, antiarrhythmic drugs, beta-blockers and catheter ablation may reduce the arrhythmic burden and alleviate symptoms, without evident impact on prevention of SCD. Selection of patient candidates to ICD implantation is the most challenging issue in the clinical management of ARVC.

This article reviews the current perspective on management of ARVC, focusing on clinical manifestations, diagnostic criteria, risk stratification and therapeutic strategies of affected patients.

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Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited heart muscle disease that predominantly affects the right ventricle (RV). It is characterized pathologically by RV myocardial atrophy with fibrofatty replacement, which acts as a substrate of ventricular electric instability with ventricular tachycardia (VT) or ventricular fibrillation (VF) that may lead to sudden cardiac death (SCD), mostly in young people and athletes.[1-4] Later in the disease course, progression of RV muscle disease and left ventricular (LV) involvement may result in heart failure. The condition was initially believed to be a developmental defect of the RV myocardium, leading to the original designation of "dysplasia." This concept has evolved over the last 25 years into the current perspective of a genetically determined "cardiomyopathy".[4] Clinical diagnosis of ARVC is often difficult because of the nonspecific nature of disease features and the broad spectrum of phenotypic manifestations. Although implantable cardioverter defibrillator (ICD) confers optimal protection against

SCD in ARVC patients, the significant rate of inappropriate interventions and complications, as well as the psychological repercussions mostly in the younger age group, argue strongly against indiscriminate device implantation.[5] However, risk stratification of affected patients is still incompletely determined.

This review article provides an up-to-date perspective on clinical manifestations, diagnosis, risk stratification and therapy of patients with ARVC.

Spectrum of clinical manifestations

The clinical phenotype of ARVC varies considerably ranging from asymptomatic family members with concealed RV structural abnormalities and no arrhythmias to patients experiencing arrhythmic cardiac arrest or undergoing cardiac transplantation due to right or biventricular heart failure.[1-4, 6-8]

Ventricular arrhythmias in the form of frequent premature ventricular beats, short runs of VT, or sustained monomorphic VT with left bundle branch block morphology, dominate the clinical scenario of the "overt arrhythmic form" of ARVC. Associated symptoms/events include palpitations, syncopal episodes (mostly occurring during physical exercise), and arrhythmic cardiac arrest due to rapid VT, which may degenerate into VF. The ECG abnormalities consist of T wave inversion and localized prolongation of QRS complex (terminal activation delay) in the precordial leads exploring

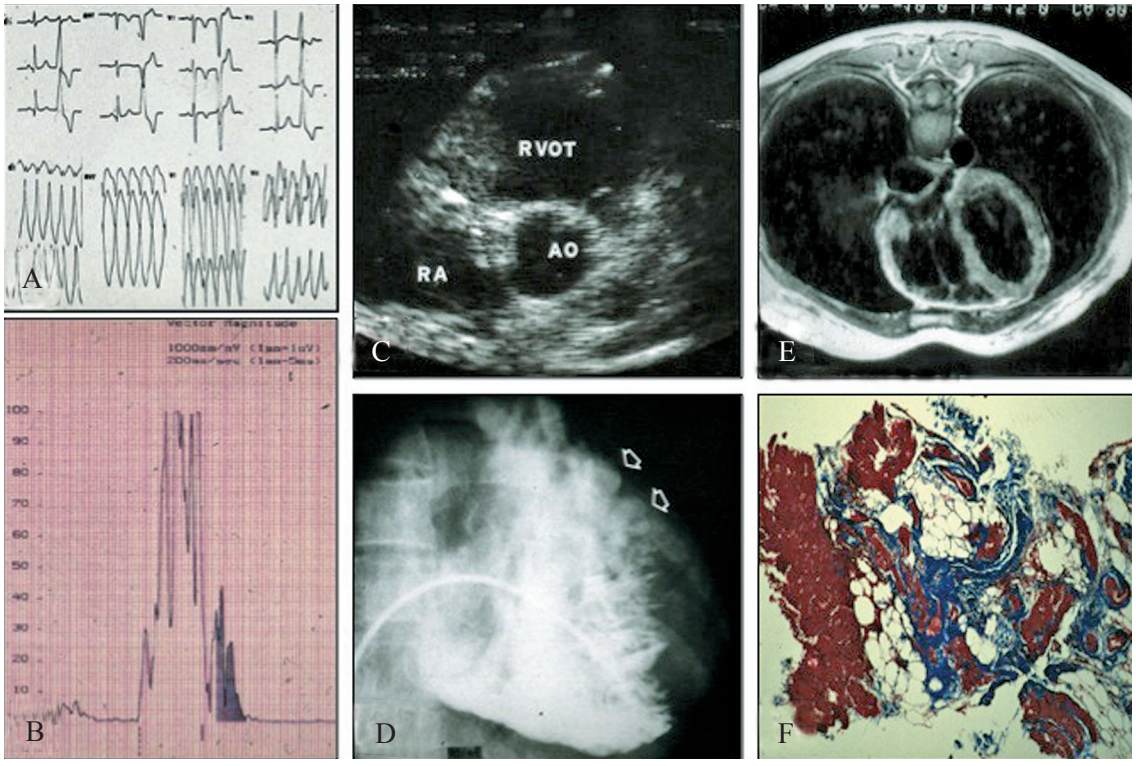

Figure 1.—Phenotypic manifestations of arrhythmogenic right ventricular cardiomyopathy.
The ARVC is characterized by a ventricular electrical instability leading to arrhythmias with a typical left-bundle branch block configuration (suggesting a right ventricular origin) (A) and electrocardiographic depolarization (delayed intraventricular conduction with QRS widening or epsilon waves in V1-V3 and late potentials on SAECG) and/or repolarization (T wave inversion) abnormalities (A, B). Morpho-functional abnormalities predominantly involve regions of the so-called "triangle of dysplasia" (right ventricular outflow tract, inflow and apex). These regions typically show diastolic bulging and/or systolic wall motion abnormalities at echocardiogram (C), ventriculography (D), or magnetic resonance (E). Endomyocardial biopsy reveals myocyte loss with fibrofatty replacement (F).
RVOT, right ventricular outflow tract. RA, right atrium. AO, aorta.

the RV (V1 to V3/V4), rarely associated with epsilon waves in advanced disease. The spectrum of RV alterations ranges from global RV dilatation/dysfunction to regional wall motion abnormalities and/or bulgings typically localized in the "triangle of dysplasia", namely subtricuspidal, apical and infundibular regions (Figure 1).[1-4, 6-8]

The LV is characteristically involved to a lesser extent, though "biventricular" or "predominant left" disease variants are increasingly reported.[1-4, 6-8] Genotype-phenotype correlation studies have identified clinical variants characterized by early and greater LV involvement, which may either parallel ("biventricular") or exceed ("left dominant") the severity of RV disease.[1-4, 6-8] This left disease variants mirror the classic ARVC phenotype, showing LV-wall motion abnormalities, T-wave inversion in the infero-lateral ECG leads and ventricular arrhythmias with a right bundle branch block morphology (suggesting a LV origin). Contrast-enhanced cardiac magnetic resonance (CE-CMR) shows the presence of LV late-gadolinium enhancement (indicating myocardial fibrosis) with a typical subepicardial/midmyocardial distribution, mostly affecting the infero-lateral LV regions. Diagnosis of left disease variants is challenging because phenotypic features overlap with those of other conditions such as dilated cardiomyopathy and myocarditis. These findings support the concept that ARVC is a heart muscle disease of the entire heart and explain the increasing use of the broader term of "arrhythmogenic cardiomyopathy", which encompasses all the disease phenotypic expressions.

Several patients with ARVC are not recognized because of lack of symptoms and subtle clinical features which are difficult to diagnose by conventional testing. In patients with "concealed form" of ARVC, the ECG may be normal or show not specific repolarization changes, along with only regional RV wall ipoakinesia without cavity enlargement. Therefore, differential diagnosis with idiopathic VT (mostly right ventricular outflow tract (RVOT) VT) by means of routine clinical tests is often not feasible, and ultimate diagnosis may depend on demonstration of fatty replacement of the RV myocardium at endomyocardial biopsy or detection of RV electroanatomic scar by endocardial voltage mapping (EVM).[9] Sudden death may be the first and definitive clinical manifestation of ARVC, mostly in young people. In this regard, a prospective clinicopathologic investigation in the Veneto Region of Italy showed that nearly 20% of fatal events in young people and athletes was due to previously undiagnosed ARVC (Figure 2).[10]

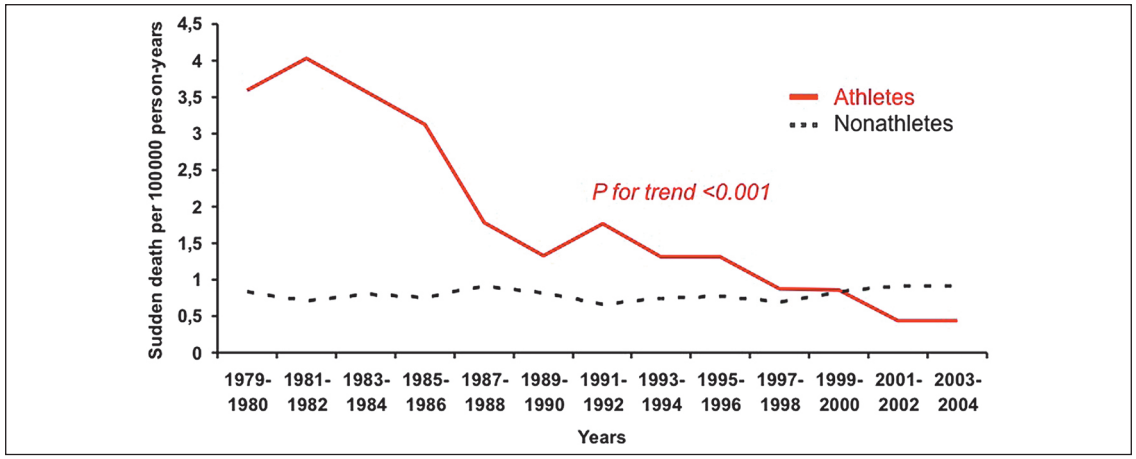

Figure 2.—Annual incidence rates of sudden cardiovascular death in Italian young competitive athletes after implementation of systematic preparticiption screening.
During the study period, the annual incidence of sudden cardiovascular death decreased by 89% in screened athletes (P for trend<0.001). In contrast, the incidence rate of sudden cardiovascular death did not demonstrate consistent changes over time in unscreened nonathletes (Veneto region of Italy, 1979-2004). Modified from Corrado *et al.*[10].

In patients with known ARVC, "RV or biventricular heart failure" may be the end-stage of the disease course as the result of progressive spreading of RV muscle disease and LV involvement that provokes global RV or biventricular dysfunction. At this stage, ARVC may mimic dilated cardiomyopathy of other causes leading to congestive heart failure and related complications such as atrial fibrillation and thromboembolic events. The diagnosis of ARVC may be not recognized at onset of symptoms in some patients who present years later with congestive heart failure, with or without ventricular arrhythmias, and are wrongly diagnosed as having idiopathic dilated cardiomyopathy.[1-4, 6-8]

Finally, clinical presentation of ARVC may simulate "acute myocarditis", characterized by chest pain, transient ST segment and T wave changes, and increased muscle enzyme levels, with or without ventricular arrhythmias.[1-4, 6-8]

Natural history

The natural history of ARVC is predominantly related to ventricular electrical instability, which may lead to arrhythmic SCD, mostly in young people and athletes. In advanced disease, progression of RV muscle disease and LV involvement may result in right or biventricular heart failure. The overall mortality rate varies among different studies, ranging from 0.08% per year during a mean follow-up of 8.5 years in the series by Nava *et al.*[11] to 3.6% per year during a mean follow-up of 4.6 years in the series by Lemola *et al.*[12] This high variability depends on the different populations considered in these studies and it reflects the wide spectrum of ARVC clinical presentations as well as the presence of subgroups with variable penetrance and SCD risk.[13-18] Of note, in a recent meta-analysis reporting data of about 600 ARVC patients who received an ICD, both for primary and secondary prevention, the annualized cardiac mortality rate was 0.9 %.[5]

The mechanism of SCD in ARVC is cardiac arrest due to sustained VT or VF, which may occur as the first manifestation of the disease in young people without previous symptoms. In the early disease phase, VF may reflect acute ventricular electrical instability related to "hot phases" of the disease, with acute myocyte death and reactive inflammation, often characterized by dynamic T-wave inversion, ST segment elevation, and myocardial enzyme release. Older patients with a long-lasting disease more often experience scar-related, re-entrant sustained VT. Ventricular arrhythmias are accentuated during or immediately after exercise, and participation in competitive athletics has been associated with an increased risk for cardiac arrest.[10] More recently, gap junction remodeling and ion channel interference preceding the fibro-fatty scar have been postulated as alternative substrates for anisotropic and delayed intraventricular conduction predisposing to lethal arrhythmias in the pre-phenotypic phase of the disease, as supported by experimental animal models.[1-4, 6-8]

The following phases in the disease natural history can be considered: 1) "Concealed" characterized by no or subtle RV structural changes, with or without minor ventricular arrhythmias, during which SCD may occasionally be the first manifestation of the disease, mostly in young people during competitive sports or intense physical exercise; 2) "Overt electrical disorder" in which symptomatic RV arrhythmias possibly leading to sudden cardiac arrest are associated with overt RV functional and structural abnormalities; 3) "RV failure" caused by the progression and extension of RV muscle disease that provoke global RV dysfunction with relatively preserved LV function. 4) "Biventricular pump failure" caused by pronounced LV involvement. At this stage, ARVC mimics biventricular dilated cardiomyopathy of other causes leading to congestive heart failure.[1-4, 6-8]

Diagnostic criteria

In 1994 standardized criteria for diagnosis of ARVC were proposed by an International Task Force.[19] The purpose was to provide diagnostic guidelines helping to overcome several problems with specificity of the ECG abnormalities, different potential aetiologies of ven-

tricular arrhythmias with left bundle branch morphology, assessment of the RV structure and function, and interpretation of endomyocardial biopsy findings. The strategy consisted in achieving clinical diagnosis by combining multiple sources of diagnostic information, such as genetic, electrocardiographic, arrhythmic, morphofunctional, and histopathologic findings. Diagnosis of ARVC would be fulfilled in the presence of two major criteria or one major plus two minor or four minor criteria from different groups. Since their publication in 1994, the Task Force criteria have been extremely useful in providing a standardized approach to clinical diagnosis of ARVC. Task Force guidelines have actually helped cardiologists to avoid misdiagnosis of ARVC in patients with dilated cardiomyopathy or idiopathic RVOT tachycardia. However, diagnostic criteria have shown to lack sensitivity for identification of early/minor phenotypes, particularly in the setting of familial ARVC. Hence, a revision of such diagnostic guidelines has been proposed with the aim to make a proper diagnosis in first degree relatives with incomplete phenotypic expression, in the setting of family screening of probands with clinically or pathologically proven ARVC.[20] In the revised Task Force diagnostic guidelines (Table I), family history criteria have been modified to include molecular genetic information. The identification of a pathogenetic gene-mutation in a first degree relative has become a major criterium for ARVC diagnosis. Of importance, revised guidelines for ARVC diagnosis also provided quantitative imaging and histopathologic measurement cut points for defining a normal RV and categorizing the various degrees of morphofunctional RV abnormalities.[20]

Genetics

The estimated prevalence of ARVC in the general population ranges from 1 in 2000 to 1 in 5000. The disease affects men more frequently than women, with an approximate ratio of 3:1 and becomes clinically overt most often in the third or fourth decade of age. A familial background has been demonstrated in 50% of ARVC cases. The disease is usually inherited as an autosomal dominant trait with incomplete penetrance and variable expression.[21-23]

Molecular genetic has provided new insights in understanding the pathophysiology of ARVC, showing that it is a desmosomal disease resulting from defective cell adhesion proteins. The first disease-causing gene, the JUP gene, was identified by McKoy *et al.* in patients with Naxos disease.[24] The gene encodes the desmosomal protein plakoglobin, a major constituent of cell adhesion junction. Its discovery suggested that ARVC is a cell-to-cell junction disease and stimulated the research in other related genes. Desmoplakin gene was the first desmosomal protein gene to be associated with the more common autosomal dominant form of ARVC by Rampazzo *et al.*[25] It was followed by the discovery of mutations in plakophilin-2 desmoglein-2 and desmocollin-2 genes, all encoding for components of cardiac desmosomes. Impaired desmosomal function results in myocardial cell-to-cell uncoupling, which leads to myocyte death and fibrofatty myocardial replacement.

Autosomal dominant ARVC has been linked to other genes unrelated to cell adhesion complex, such as the gene encoding for cardiac ryanodine receptor, which is responsible for calcium release from the sarcoplasmic reticulum, and the transforming growth factor-β-3 gene, which regulates the production of extracellular matrix components and modulate expression of genes encoding desmosomal proteins.[26-31]

The availability of molecular testing for mutation screening of desmosomal genes offers the possibility to identify genetically affected individuals. At the present time, the role of molecular genotyping for diagnosis of ARVC of index cases with "borderline" or "possible" ARVC is limited by the complex genetic background of the disease which accounts for our current difficulty in identifying true disease-causing gene defects.[8] The major advantage of molecular genotyping is the possibility to make a preclinical diagnosis of ARVC in the setting of a familial disease, when the proband carries an identified pathogenetic desmosomal

TABLE I.—*Original versus Revised Task Force Criteria for diagnosis of ARVC.*

Original Task Force Criteria	Revised Task Force Criteria
I. Global or regional dysfunction and structural alterations*	
Major	Major
Severe dilatation and reduction of RV ejection fraction with no (or only mild) LV impairment – Localized RV aneurysms (akinetic or dyskinetic areas with diastolic bulging) – Severe segmental dilatation of the RV	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% 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% By RV angiography: – regional RV akinesia, dyskinesia, or aneurysm
Minor	Minor
Mild global RV dilatation and/or ejection fraction reduction with normal LVMild segmental dilatation of the RV Regional RV hypokinesia	By 2D echo: – 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 m/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: – 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%
II. Tissue characterization of wall	
Major	Major
– Fibrofatty replacement of myocardium on endomyocardial biopsy	– 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
Minor	Minor – Residual myocytes 60% to 75% by morphometric analysis (or 50% to 65% if estimated), with fibrous replacement of the RV free wallmyocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy
III. Repolarization abnormalities	
Major	Major Inverted T waves in right precordial leads (V1, V2, and V3) or beyond in individuals >14 years of age (in the absence of complete right bundle-branch block QRS ≥120 ms)
Minor – Inverted T waves in right precordial leads (V2 and V3) (people age >12 years, in absence of right bundle-branch block)	Minor – Inverted T waves in leads V1 and V2 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 V1, V2, V3, and V4 in individuals >14 years of age in the presence of complete right bundle-branch block

(to be continued)

TABLE I.—*Original versus Revised Task Force Criteria for diagnosis of ARVC (Continues).*

Original Task Force Criteria	Revised Task Force Criteria
IV. Depolarization/conduction abnormalities	
Major – Epsilon waves or localized prolongation (>110 ms) of the QRS complex in right precordial leads (V1 to V3)	Major – Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V1 to V3)
Minor – Late potentials (SAECG)	Minor – 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 V1, V2, or V3, in the absence of complete right bundle-branch block
V. Arrhythmias	V. Arrhythmias
Major	Major – 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)
Minor – Left bundle-branch block–type ventricular tachycardia (sustained and nonsustained) (ECG, Holter, exercise) – Frequent ventricular extrasystoles (>1000 per 24 hours) (Holter)	Minor – Nonsustained or sustained ventricular tachycardia of RV outflow configuration, left bundle-branch block morphology with inferior axis (positive QRS in leads II, III, and aVF and negative in lead aVL) or of unknown axis – >500 ventricular extrasystoles per 24 hours (Holter)
VI. Family history	VI. Family history
Major – Familial disease confirmed at necropsy or surgery	Major – ARVC/ confirmed in a first-degree relative who meets current Task Force criteria – ARVC confirmed pathologically at autopsy or surgery in a first-degree relative – Identification of a pathogenic mutation† categorized as associated or probably associated with ARVC in the patient under evaluation

PLAX: parasternal long-axis view; RVOT: RV outflow tract; BSA: body surface area; PSAX: parasternal short-axis view.
*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 that alters or is expected to alter the encoded protein, is unobserved or rare in a large non–ARVC 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. Modified from *Marcus et al.*[20]

gene mutation. It is important to remember that molecular genetic testing may only support but cannot make diagnosis of ARVC itself.[7, 8] Inheriting a mutation does not mean that the individual will present an overt disease phenotype. In fact, mutations carriers may either have no disease phenotype (incomplete penetrance) or present clinically with minor clinical manifestations (variable expression). This suggests that a positive genetic result can only be part of a more comprehensive clinical approach combining multiple sources of diagnostic information such as ECG changes, ventricular arrhythmias, RV structural and functional alterations, histopathogic abnormalities, and clinical and molecular genetic findings.[7, 8]

ECG abnormalities

ECG abnormalities are detected in up to 90% of ARVC patients; T-waves inversion in the precordial leads exploring the right ventricle (V1-V3) is the most common finding.[1-4] These repolarization abnormalities are

not pathognomonic of ARVC since may be a normal variant in females and in children aged less than 14 years, or may be secondary to a right bundle branch block. The ECG abnormalities resulting from delayed RV activation include complete or incomplete right bundle branch block, prolongation of right precordial QRS duration (terminal activation delay), and postexcitation epsilon waves (*i.e.* small amplitude potentials occurring after the QRS complex at the beginning of the ST segment).[1-4] Activation delay can be also detected in the form of late potentials in the terminal portion of the QRS complex by signal averaging techniques. Both epsilon waves and late potentials reflect areas of slow intraventricular conduction, which may predispose to re-entrant ventricular arrhythmias. The underlying substrate consists of islands of surviving myocardium interspersed with fatty and fibrous tissue, accounting for fragmentation of the electrical activation of the ventricular myocardium. In ARVC, late potentials are correlated with the extension of RV involvement and with the disease progression.

Ventricular arrhythmias

The spectrum of ventricular arrhythmias in ARVC ranges from isolated premature ventricular beats to sustained VT or VF leading to sudden cardiac arrest.[1-4] The arrhythmia severity varies both from patient to patient and during the course of the disease. The distinctive QRS morphology of ventricular arrhythmias is left bundle branch block, which indicates an origin from the RV. Moreover, the mean QRS axis suggests the site of origin: inferior axis the RVOT, superior axis the RV inferior wall or the apex. Patients with advanced and widespread ARVC may show several morphologies of VT, indicating multiple arrhythmogenic foci. It is often difficult to differentiate ARVC from idiopathic RVOT tachycardia, which is usually benign and non-familial. It is still debated whether some cases of RVOT tachycardia represent a form fruste of ARVC, as suggested by underlying segmental RV structural abnormalities detected by either CMR or EVM.

VF is relatively rare in patients with known ARVC undergoing medical treatment for symptomatic VT, although some cases of rapid, hemodinamically unstable or prolonged VT may degenerate into VF. On the other hand, abrupt VF is the most likely mechanism of instantaneous sudden death in previously asymptomatic young people and athletes with ARVC. Whether VF in this subset of patients is related to an acute phase of disease progression, either due to myocyte necrosis-apoptosis, or inflammation remains to be established.[1-4, 6-8]

Functional and structural ventricular alterations

Relevant structural and functional abnormalities include global RV dilatation, with or without ejection fraction reduction, and regional RV dilatation/dysfunction such as akinesia, dyskinesia and bulgings.[1-4, 6-8] In the past, RV angiography was regarded as the gold standard for the diagnosis. Angiographic evidence of akinetic or dyskinetic bulgings localized in infundibular, apical, and subtricuspidal regions, has a high diagnostic specificity (over 90%). Compared with contrast angiography, echocardiography is a noninvasive and widely spread technique, and represents the first line imaging approach in evaluating patients with suspected ARVC or in screening family members. Echocardiography also allows serial examinations aimed to assess the disease progression during the follow up of affected patients. Other than a visual assessment of wall motion and structural abnormalities, a quantitative echocardiographic evaluation of the RV including measurements of endiastolic cavity dimensions (inlet, outlet, and mean ventricular body), wall thickness, volume and function is mandatory in order to enhance the diagnostic accuracy. CE-CMR imaging has become in the recent years an integral part of diagnostic work-up of ARVC. Besides evaluating the presence of morpho-functional ventricular abnormalities, CE-CMR allows myocardial tissue characterization by late gadolinium enhancement technique, which provides information on the presence, morphology and wall distribution of

myocardial fibrofatty scar, the hallmark lesion of ARVC.

All the above imaging techniques appear to be accurate in detecting RV structural and functional abnormalities in overt form of ARVC, but they are less sensitive in detecting subtle lesions. Therefore, the diagnosis of ARVC at its early stages or in its concealed variants remains a clinical challenge by all imaging methods.[6-8]

Endomyocardial biopsy

Endomyocardial biopsy has the potential for an *in vivo* demonstration of typical fibrofatty replacement of the RV muscle and may increase the accuracy for the clinical diagnosis of ARVC, even though it has several diagnostic limitations.[32] The sensitivity of endomyocardial biopsy is low because to avoid risk of perforation the myocardial samples are taken from the septum, a region uncommonly involved by the disease. On the other hand, there is difficulty in differentiating ARVC from either other causes of fatty infiltration of the RV myocardium or the normal amount of subepicardial adipous tissue, which has been reported in the human heart. Endomyocardial biopsy cannot be routinely recommended and should be reserved to selected patients in whom final diagnosis depends on histologic exclusion of other cardiomyopathies or myocarditis, such as sarcoidosis.[32]

Risk stratification

Once the diagnosis is made, the major clinical target is prevention of SCD by identifying high-risk patients who are candidates for ICD therapy, the only proven lifesaving treatment of ARVC. The role of ICD therapy in patients with overt disease and high risk of SCD (survivors from a cardiac arrest and patients with sustained VT) is well established.[33, 34] The revised International Task Force diagnostic criteria and the growing use of molecular genetic screening allowed to identify a growing population of patients with early/minor disease phenotypes and healthy gene carriers who have a definitively lower risk of SCD. In this subset of patients with a mild clinical phenotype the indication for ICD implantation is still a matter of debate.

Studies on ICD therapy

Many studies demonstrated that ICD is the most effective therapy for prevention of SCD in ARVC. Although no data from randomized trials are available, a number of observational longitudinal studies support the current perspective that ICD improves long-term prognosis and survival when implanted in selected patients at high risk of SCD. These studies provided significant insights on ICD-therapy-based risk stratification and allowed identification of clinical and electrophysiological markers, which may predict the occurrence of appropriate shocks against life threatening ventricular arrhythmias in patients who received an ICD for either primary or secondary prevention of SCD.

The first study to demonstrate the survival benefit of ICD in ARVC was the Darvin I study.[33] It was a multicenter prospective study enrolling 132 patients with ARVC who underwent ICD implantation, mostly (88%) because of history of cardiac arrest, sustained VT or syncope (secondary prevention). During a follow-up of more than 3 years, 48% of the population experienced an appropriate ICD intervention. In Figure 3, the Kaplan-Meier curve of actual patient survival is compared with the Kaplan-Meier curve of survival free of VF/ventricular flutter (Vfl) that in all likelihood would have been fatal in absence of ICD. Divergence between lines reflects the estimated survival benefit of ICD therapy (estimated mortality reduction at 36 months of 24%). Patients who received ICD because of cardiac arrest or VT with hemodynamic compromise showed a high incidence of VF during follow-up (10% per year of follow-up): of note, also patients with a previous history of unexplained syncope had a similar high incidence of fatal arrhythmic events (8% per year of follow-up) (Figure 4). At multivariate analysis history of cardiac arrest or VT with hemodynamic com-

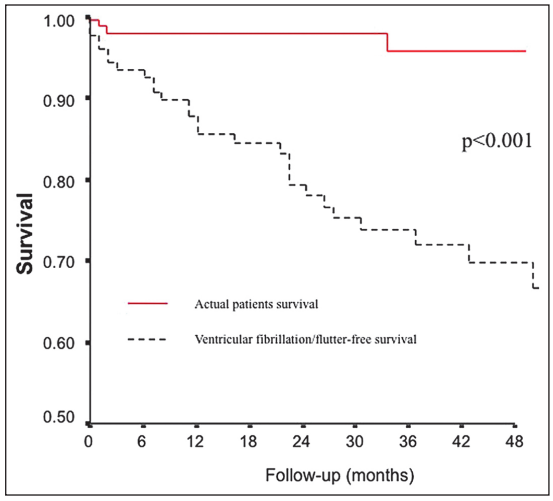

Figure 3.—Darvin I study.
Kaplan-Mayer analysis of actual patient survival compared with survival free of ventricular fibrillation/flutter that in all likelihood would have been fatal in the absence of the ICD. The divergence between the lines reflects the estimated mortality reduction by ICD therapy of 24% at 3 years of follow-up. Modified from Corrado *et al.*[33]

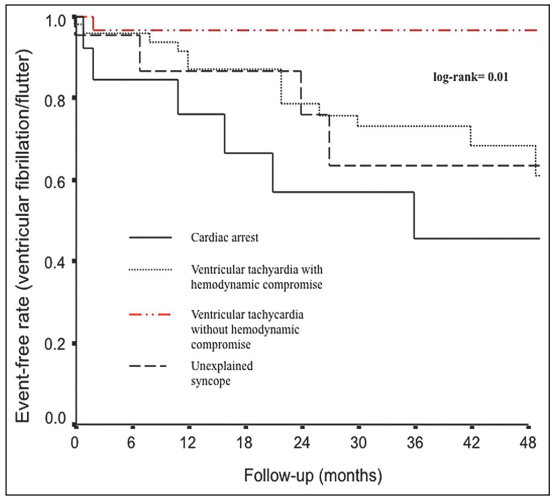

Figure 4.—Darvin I study.
Kaplan-Mayer curves of freedom from ICD interventions on ventricular fibrillation/flutter for different patient subgroups stratified for clinical presentation. Patients presenting with ventricular tachycardia without hemodynamic compromise had a significantly lower incidence of ventricular fibrillation/ventricular flutter during the follow-up (1% per year of follow-up) than those implanted because of cardiac arrest or ventricular tachycardia with hemodynamic compromise (10% per year of follow-up) or unexplained syncope (8% per year of follow-up). Modified from Corrado *et al.*[33]

promise, decreasing age and reduced LV ejection fraction were independent predictors for VF/Vfl.[33]

In the study by Hulot *et al.*,[34] 130 patients with ARVC were enrolled with the purpose to identify risk factor for long-term prognosis. During a mean follow-up of 8 years, 24 patients died (21 from cardiovascular death), with an annual mortality rate of 2.3%. Clinical signs of RV failure and LV dysfunction were independently associated with cardiovascular deaths. Accordingly, the following risk stratification algorithm was proposed, based on the identification of 3 groups. Group 1 included patients presenting with no VT and no clinical signs of heart failure, Group 2 patients who experienced VT in the absence of heart failure and Group 3 patients with both a history of VT and right ventricular failure and/or LV dysfunction. Patients of the Group 1 with a low risk profile did not experience any cardiovascular death during follow-up. On the contrary, high-risk patients of the Group 3 had a significant annual mortality rate of 4.7%. Because the authors did not evaluate separately risk factors for heart failure death from those for SCD, specific predictors of adverse arrhythmic outcome could not be determined.

Clinical predictors of SCD in the subgroup of patients with ARVC who did not experience cardiac arrest or VT (primary prevention) were investigated by the multicenter observational study by Corrado *et al.* ("Darvin II" study).[35] The study enrolled patients who received an ICD for the following reasons: 1) history of premature SCD in one or more first-degree relatives, 2) non sustained VT (NSVT) on exercise testing and/or 24-hour ambulatory Holter ECG monitoring, 3) prior syncope, and/or 4) inducibility at programmed ventricular stimulation (PVS). During a mean follow-up of 5 years, 25 (24%) patients had appropriate ICD interventions despite antiarrhythmic drug therapy. Based on the analysis of the stored electrograms, 17 (16%) received life-saving shocks against VF or Vfl. The estimated annual event rate of life–saving ICD interventions was ~3%. Figure 5 shows Kaplan Meier analysis comparing the actual patient survival and VF/Vfl-free patient survival.

Compared with the 100% actual survival rate at 48 months, VF/Vfl-free survival rates was 77% at 48 months of follow-up; the estimated mortality reduction at 48 month was 23% and the divergence between the two curves reflects the estimated survival benefit of ICD implantation. The analysis was based on the assumption that ICD interventions against VF/Vfl are live-saving, unlike those against stable VT. On multivariate analysis, syncope was the only independent predictor of appropriate ICD interventions (9% annual rate) (Figure 6). On the contrary, patient implanted because of a family history of SCD did not receive any appropriate ICD discharge.

A US single center study from Bhonsale *et al*.[36] analyzed a population of 84 patients who received an ICD for primary prevention, with the aim to identify clinical predictors of ICD therapy. During a follow-up of 4 years, almost half population (48%) experienced an appropriate ICD intervention, with an annual event rate of 10%, which was much higher than that found in the Darvin II study (4.8%/year). Only 19% of the patients received an ICD intervention for VF, with an annual event rate of 4%, which was similar to that reported by Darvin II study (3.3%/year). Proband status, premature ventricular contractions (PVC)>1000/24 hours, NSVT and inducibility during electrophysiological study (EPS) were univariate predictors of appropriate ICD interventions; however, on multivariate analysis the only independent predictor of appropriate ICD interventions remained inducible VT/VF. Of interest, the study demonstrated that the presence of multiple risk factors substantially increased the risk of appropriate ICD interventions. While patients with ≤ 1 risk factor did not receive any appropriate ICD therapy, 78% of patients with 4 risk factors experienced appropriate ICD interventions.

The study of Link *et al.*[37] enrolled 137 consecutive ARVC patients (108 with an ICD). The study purpose was to find predictors of ventricular arrhythmias and to identify the best antiarrhythmic treatment. In patients with an ICD, risk factors for arrhythmic events during follow-up were sustained VT before ICD implantation and T-wave inversion in inferior leads. The only independent predictor for life-threatening arrhythmias was the young age at enrolment. Of note, any inducible VT/VF at preimplant P*VS.* was unable to predict the arrhythmic outcome. It was also demonstrated that in patients with ICD, antitachycardia pacing (ATP) was highly successful in terminating VT, suggesting that this therapeutic modality should be available and active in all patients, regardless of the rate of ventricular tachyarrhythmias.

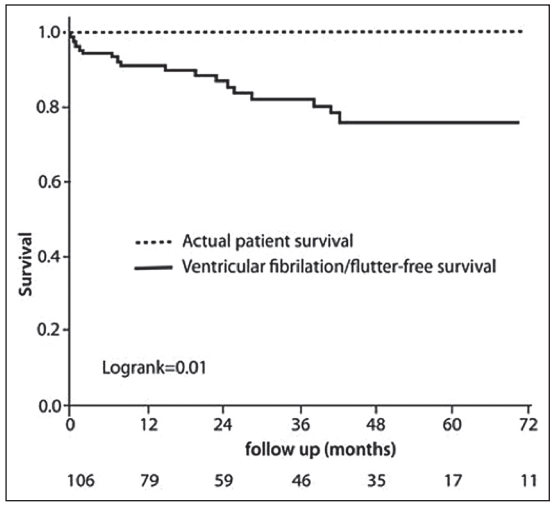

Figure 5.—Darvin II study.
Kaplan-Meier analysis of survival free of ventricular fibrillation/ventricular flutter that in all likelihood would have been fatal in the absence of the ICD compared with actual patient survival. Divergence between lines reflects the estimated survival benefit of ICD therapy (23% at 48 months of follow-up). Modified from Corrado *et al.*[35]

Risk factors

The following clinical variables were identified in at least one published study as independent predictors of poor arrhythmic outcome at multivariate analysis.

The importance of ECG in the diagnosis of ARVC is well established, but it plays a role also in defining the disease prognosis. Among ECG parameters, greater extent of T wave inversion across the twelve leads has been associated with poorer arrhythmic prognosis. This finding may be explained by demonstration

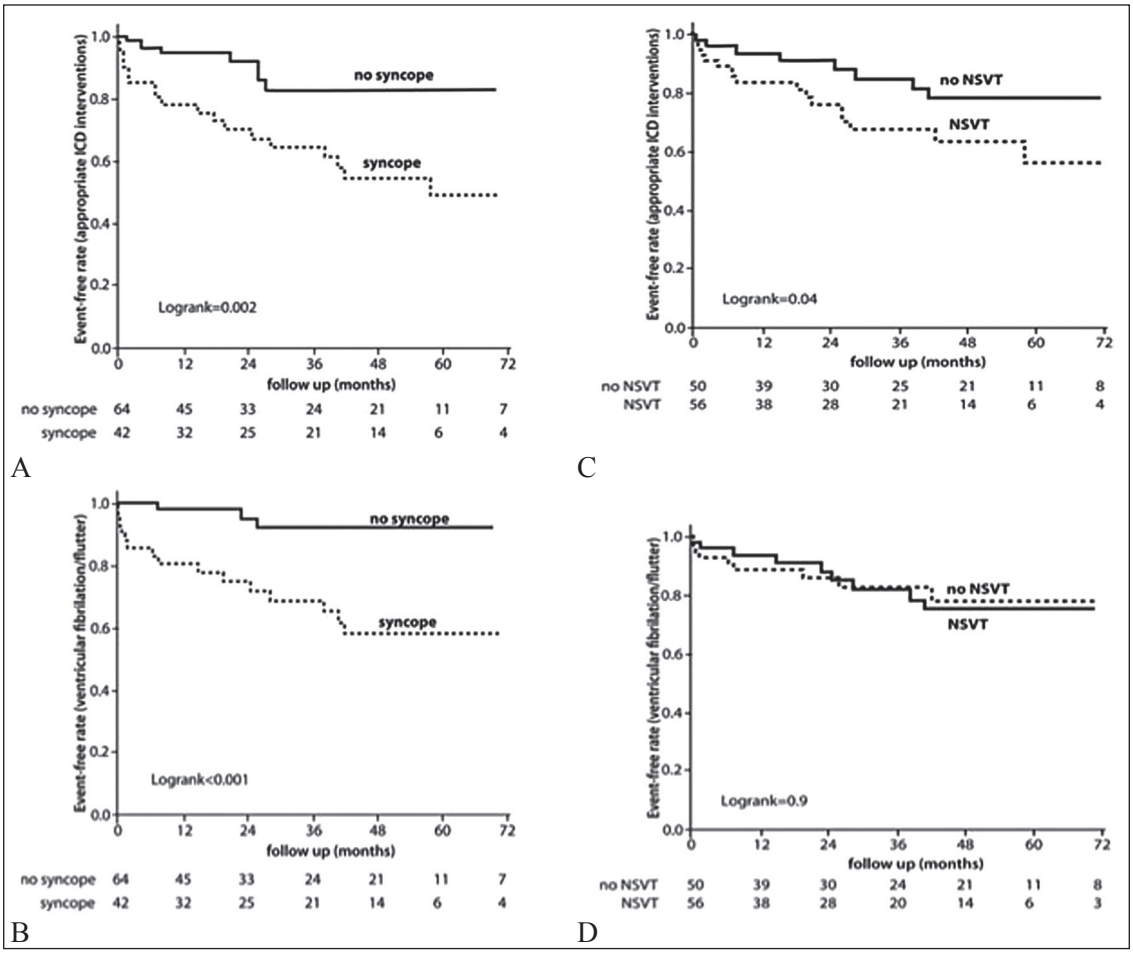

Figure 6.—Darvin II study.
Kaplan-Meier analysis of freedom from any appropriate ICD interventions (A) and shock therapies on ventricular fibrillation/flutter (B) stratified by syncope. Kaplan-Meier analysis of freedom from any appropriate ICD interventions (C) and shock therapies on ventricular fibrillation/flutter (D) stratified by non-sustained ventricular tachycardia A significantly different rate of appropriate ICD interventions was observed in patients with prior syncope and non-sustained ventricular tachycardia. Patients with prior syncope had a significantly higher cumulative rate of shocks on ventricular fibrillation/flutter. NSVT, non-sustained ventricular tachycardia. Modified from Corrado *et al.*[35]

that the extent of negative waves across ECG leads predicts the severity of RV fibro-fatty scar, which acts as a substrate for ventricular tachyarrhythmias in ARVC.[38] Saguner *et al*. [17] analyzed 111 ECG of ARVC patients to find ECG abnormalities able to predict adverse events during follow up. They found that a precordial QRS amplitude ratio of ≤0.48, inferior leads T-wave inversions and QRS fragmentation were independent predictors of a poor outcome. The study from Link *et al.*[37] found a significant association between ventricular arrhythmias during follow-up and T-wave inversions in the inferior leads. In another study from Bhonsale *et al*.,[15] the presence at the basal ECG of inverted T-wave in ≥3 precordial leads was an independent predictor of the first arrhythmic event on multivariable analysis.

The value of syncope as a prognostic factor for SCD was first reported by Marcus *et al.;*[39] they suggested a more adverse long-term prognosis in those patients with history of syncope. The role of syncope for risk stratification was then demonstrated in other studies. In the Darvin I and II studies,[33, 35] "unexplained" syncope was defined as a loss of conscious-

ness not requiring electric cardioversion for recovery that: 1) occurs in the absence of documented ventricular arrhythmias and/or circumstances clearly leading to reflex-mediated changes in vascular tone or heart rate such as a micturition, defecation, cough, or other similar conditions; and 2) remains unexplained after a detailed clinical evaluation aimed to exclude other cardiac or extracardiac causes. The Darvin I study [33] demonstrated that patients presenting with unexplained syncope have a similar annual rate of life-saving ICD interventions (8% per year of follow-up) of patients who received an ICD for cardiac arrest or VT with hemodynamic compromise (10% per year of follow-up). In the Darvin II study,[35] the strongest predictor of ICD therapy in ARVC patients with no prior cardiac arrest or sustained VT was a history of syncope. At multivariate analysis, syncope resulted not only an independent predictor of appropriate ICD interventions and but also the unique independent predictor of shock therapy on VF/Vfl. At variance, in the study from Bhonsale *et al.*,[36] the presence of syncope was not a predictor of appropriate ICD interventions, although a history of recent or unexplained syncope was able to identify a subgroup of patients with a higher risk of ventricular arrhythmias. Of note, patients with syncope had a high rate (9%/year) of appropriate ICD therapy. These data indicate that syncope should be regarded as a warning sign, because most episodes are secondary to potentially life-threatening ventricular tachyarrhythmia.

Ventricular arrhythmias are the most typical clinical manifestation of ARVC. In the Darvin I study [33] prior cardiac arrest caused by VF and hemodynamically instable VT were demonstrated to be independent predictors for life-saving ICD interventions. In the Darvin II [35] study NSVT were significantly associated with appropriate ICD interventions on any ventricular tachyarrhythmia, but they were not predictors of appropriate ICD intervention on VF/Vfl. Bhonsale *et al.* [36] also demonstrated that on univariate analysis NSVT and PVC>1000/24h were predictors of appropriate ICD discharge. NSVT was the only independent predictor of appropriate ICD interventions on multivariable analysis. The value for predicting "life-saving" ICD interventions was not reported in this study.

Structural and functional alterations of the RV are a key phenotypic feature of ARVC. Both autopsy series and clinical imaging studies show that the LV is often involved, leading to the current perspective that ARVC is a biventricular disease.[7, 40] Hulot *et al.* [34] reported single-center, long-term follow-up data on the natural history and risk stratification of 130 ARVC patients. Ten patients received an ICD; twenty-four patients died during a follow-up of 8.1±7.8 years, resulting in an annual mortality rate of 2.3%. No death occurred in patients with an ICD. In twenty-one patients there was a cardiovascular death (7 SCD and 14 due to progressive heart failure). Six of 10 patients with an ICD received at least 1 appropriate shock. The presence of VT with a left bundle branch block pattern was associated with cardiovascular death. Clinical signs of RV failure and LV dysfunction, but not VT, were independently associated with cardiovascular death. The results of this single center study unexpectedly demonstrated that heart failure was the major cause of death in ARVC. In the ICD studies from Wichter *et al.* [41] and from Rougin *et al.*,[42] severe RV dysfunction was found to be an independent predictor for appropriate device discharge.

When considering the role of EPS in the diagnosis and management of ARVC it is important to recognize that EPS can serve many functions. First, it is well recognized that benign idiopathic RVOT tachycardia is frequently misdiagnosed as ARVC. The importance of distinguishing these two conditions cannot be underestimated. Whereas idiopathic VT is a benign condition that is not inherited and is curable with catheter ablation, ARVC is an inherited, life-threatening disease that may require placement of an ICD for SCD prevention. In this context, one of the most important roles of an EPS study is to help distinguish these two conditions. If an idiopathic VT is present, curative catheter ablation can be performed at the time of an initial diagnostic EPS study.[9] Sec-

ond, an EPS may provide information regarding the inducibility of one or more VTs with different rates and/or morphologies as well as identification of overlap of rate between VTs and supraventricular tachyarrhythmia. This facilitates the diagnosis of ARVC and optimization of VT detection/discrimination algorithms and programming of more effective ATP protocols in patients treated with an ICD.[41] The third potential role of an EPS is for risk stratification. However, conflicting data exists concerning the value of inducibility of sustained VT as a predictor of long-term arrhythmic outcome.[33, 35-37, 43] The largest multicenter studies on ARVC patients who received an ICD reported that the incidence of "life-saving" ICD discharges for treatment of fast VT or VF did not differ significantly in patients who were and were not inducible at PVS, regardless of the specific indication for ICD implantation.[33, 35] These studies suggest that EPS is of limited value in identifying patients at risk of arrhythmic cardiac arrest because of a low predictive accuracy. This is in agreement with the recognized limitation of EPS for arrhythmic risk stratification of other non-ischemic heart diseases such as hypertrophic and dilated cardiomyopathy. In the study of Wichter *et al.*,[41] induction of VT/VF at pre-implant EPS in patients who received an ICD because of a previous history of cardiac arrest or sustained VT, demonstrated a trend toward statistical significance for subsequent appropriate device interventions. In the cohorts of ARVC patients reported in other studies, inducibility at P*VS.* was a significant predictor of appropriate ICD firing. However, in the Bhonsale study [36] the positive and negative predictive values of P*VS.* inducibility were 65% and 75%, respectively, and a sizeable proportion of patients experienced ICD interventions during follow-up despite a lack of inducibility of VT/VF. Moreover, the predictive value of inducibility at P*VS.* for life-saving ICD discharges on fast VT or VF was not demonstrated in the study by Bhonsale *et al.* by either univariate or multivariate analysis.[36]

Endocardial voltage mapping is an emerging tool that is useful in establishing a diagnosis of ARVC as it can identify and quantify RV regions of scar with low-amplitude electric signals which typically show fractionation, double potentials, or conduction delay.[9] Recent prospective studies showed that demonstration and quantification of bipolar RV electroanatomic scar area [44] as well as identifications of scar-related fractionated electrograms and late potentials [45] provide significant added value for arrhythmic risk assessment in ARVC (Figure 7). Because EVM is an invasive, expensive and highly operator-dependent technique with a significant risk of inaccurate interpretation of low-voltage recordings in areas of normal myocardium due to suboptimal catheter contact, it is not recommended as a routine diagnostic tool. The arrhythmic prognostic value of EVM technique remains to be confirmed by larger studies.

Although many advances have been made in our understanding of the genetic background of ARVC, the use of molecular genetic testing for risk assessment is of limited value.[8] With the exception of the rare ARVC5 variant, which is characterized by a defect of TMEM43 gene, encoding for a transmembrane protein, and associated with a fully penetrant and lethal disease,[28] studies of genotype-phenotype correlation have shown that neither specific desmosomal genes nor type of mutations are predictive of outcome.[8] Most importantly the study of Rigato *et al.* demonstrated that a complex genotype with multiple desmosomal mutations (compound/digenic heterozygosity) was significantly associated with a more severe long-life arrhythmic outcome (double-dose effect). In this study, both multiple gene mutations and male sex were independent risk factors for occurrence since birth of major arrhythmic events. These findings highlight the importance of screening the entire panel of desmosomal genes even after a single gene mutation has been identified.

No studies found that family history of SCD "per se" significantly predicts an adverse clinical course. In the Darvin II study,[35], none of the 27 patients who received an ICD because of isolated family history of SCD experienced appropriate ICD discharges during the follow-up.

Clinical management and therapy

The most important objectives of clinical management of ARVC patients include: 1) reduction of mortality, either by arrhythmic SCD or death from heart failure; 2) prevention of disease progression leading to RV-, LV- or biventricular-dysfunction and heart failure; 3) improvement of symptoms and quality of life by reducing/abolishing palpitations, VT recurrences or ICD discharges (either appropriate or inappropriate); and 4) limiting heart failure symptoms and increasing exercise capacity. Therapeutic options include pharmacologic treatment, catheter ablation, ICD, and heart transplantation.[46]

Life style changes

In ARVC patients competitive and/or endurance training must be avoided; this restriction may also be considered in ARVC family members with a negative phenotype. The rationale for these recommendations is that sports activity has been proven to increase by fivefold the risk of SCD in young ARVC patients. Sport is not "per se" the cause of increased mortality, but it acts as a trigger of fatal ventricular arrhythmias in the presence of an underlying cardiovascular disease like ARVC.[47] Moreover, physical exercise may promote phenotyopic expression and/or accelerate disease progression. Experimental and clinical studies demonstrated that physical activity favors the development of RV dysfunction and dilatation, anticipates the occurrence of clinical manifestations and increases age-related penetrance in desmosomal genes carriers (Figure 8).

Antiarrhythmic drugs

There are no prospective and randomized trials on antiarrhythmic drug (AAD) therapy in ARVC and systematic comparison of treatment strategies. Moreover, the assessment of efficacy of specific AAD therapy is difficult because ARVC patients tend to have multiple arrhythmic events over time and drugs are often changed. Available data are limited to case-control studies, retrospective analyses, and clinical registries. Hence, indication for AAD therapy and choice of drug are based on an empirical approach resulting from extrapolation from other diseases, personal experience, and consensus/individual decisions.[46]

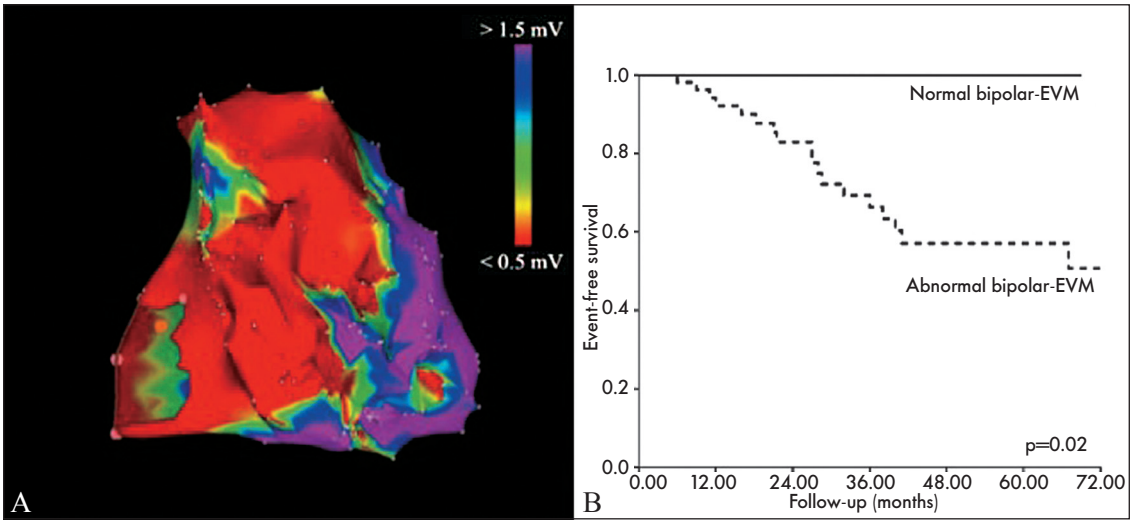

Figure 7.—Endocardial voltage mapping.
Antero-posterior view of bipolar endocardial voltage mapping featuring a large right ventricular electroanatomic scar involving the antero-lateral, RV outflow tract, and infero-basal regions (A). Kaplan–Meier analysis of freedom from adverse events stratified by the presence of abnormal bipolar endocardial voltage mapping. Overall, the annual event rate was 11.4%/y in patients with an abnormal bipolar endocardial voltage mapping and 0%/y with a normal bipolar endocardial voltage mapping. EVM, endocardial voltage mapping (B). Modified from Migliore *et al.*[44]

The available evidence suggests that sotalol and amiodarone (alone or in combination with beta-blockers) are the most effective drugs with a relatively low proarrhythmic risk, although their ability to prevent SCD is unproven. The largest European non-randomized study on the efficacy of AAD therapy in ARVC was published by Wichter *et al*. in 1992 [48] and updated in 2005.[49] In the initial series, among 81 patients undergoing P*VS.* in AAD free-state, VT was inducible in 42 patients and not inducible in 39 patients. Antiarrhythmic drugs were administered in both groups and acute and long-term drug efficacy was tested by serial electro-pharmacological P*VS.* in inducible patients and by non-invasive Holter monitoring and exercise test in non-inducible patients. In the inducible patients, acute success rate was 68.4% for sotalol, 15% for amiodarone, 15.4% for the combination therapy (*i.e.* class I and sotalol or amiodarone) and 5.6%-12% for single Class I AADs. Beta-blockers and verapamil alone showed no efficacy. Thirty-one (73.8%) of these inducible patients were discharged with AAD therapy including 21 patients taking sotalol alone and 4 patients treated with sotalol in association with class I AADs. During a mean follow-up of 34 months, there were no deaths, while 3 patients (9.7%) had non-fatal recurrence of VT. In the non-inducible patient subgroup sotalol showed a success rate of 82.8%, beta-blockers of 28%, amiodarone of 25%, and AADs combination therapy of 9.1%; class I AADs alone were rarely effective. During a mean follow-up of 14 months there were no cardiac deaths and 4 patients (12.1%) had non-fatal recurrences of VT. In this study sotalol at a dose of 320-480 mg/day (up to 640 mg/day in selected cases) was the most effective AAD therapy for inducible and non-inducible VT in ARVC patients. Amiodarone was less effective and showed a high incidence of extracardiac side effects during long-term follow-up and beta-blockers were effective only in non-inducible patients. Wichter *et al.* (48), provided updated results on 191 patients which confirmed that sotalol was the most effective drug resulting in 68% overall efficacy, followed by the combination of amiodarone and beta-blockers.

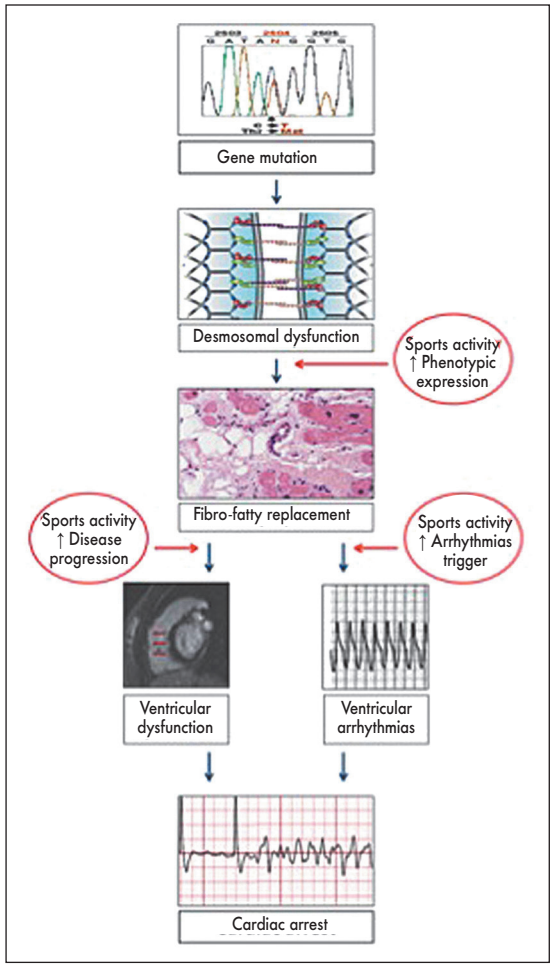

Figure 8.—Schematic representation of ARVC course from desmosomal-gene mutation to phenotypic expression and cardiac arrest due to ventricular fibrillation.
Sports activity may promote development of phenotypic expression, accelerate disease progression and trigger life-threatening ventricular arrhythmias.

An observational study by Marcus *et al.*[50] examined the efficacy of empiric AADs in a rigorously characterized cohort of ARVC patients in the USA. Only the small subgroup of patients receiving amiodarone had a significantly lower rate of appropriate ICD interventions for ventricular tachyarrhythmia, while neither beta-blockers nor sotalol seemed to be protective. Discrepancy between the Marcus'study and previous studies reporting a greater efficacy of sotalol may be related to different study populations (high risk patients

with an ICD *vs.* low/intermediate risk patients without an ICD), drug doses (160-320 *vs.* 320-480 mg/day), therapeutic approach (empiric *vs.* guided by EPS/Holter), and follow-up duration (16±13 *vs.* 52±34 months).

Of the 132 ARVC patients with an ICD reported by Corrado *et al.*,[35] 104 (79%) received concomitant AAD therapy which consisted of sotalol (36%), amiodarone either alone (8%) or in combination with beta-blockers (13%), beta-blockers (20%), or flecainide (2%). During a follow-up of 39±25 months, 64 of 132 patient (48%) had appropriate ICD intervention; 53 of these 64 patients (83%) were receiving AAD therapy at the time of first ICD intervention, compared with 51 of 68 patients (75%) with no or inappropriate interventions. The incidence of VF and Vfl, which may have been fatal in the absence of the ICD, was neither significantly different between patients who did and did not receive AAD therapy nor between patients treated with different AADs, regardless of clinical presentation. These findings indicate that the majority of life-saving ICD interventions in high risk patients occurred despite concomitant AADs and support the concept that AAD therapy may not confer adequate protection against SCD.

Since there is no proof that AAD therapy prevents SCD, its use is indicated only to reduce symptoms and improve quality of life. AADs are recommended to reduce ICD appropriate discharge or the occurrence of hemodynamically stable VT in patients who underwent catheter ablation. AAD therapy should be also considered to improve symptoms in case of premature ventricular ectopic beats or non-sustained VT.[46]

Beta-blockers

Beta-blockers are recommended in patients with recurrent appropriate ICD discharges against ventricular tachyarrhythmias as well as to reduce inappropriate ICD interventions due to supraventricular arrhythmias. Beta-blocker therapy is also indicated in asymptomatic patients due to its ability to prevent exercise-induced ventricular arrhythmias and to hinder myocardial disease progression by lowering the ventricular wall stress.[46]

Heart failure therapy

Standard heart failure pharmacological treatment (angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers and diuretics) is recommended in ARVC patients who developed RV o biventricular symptomatic dysfunction; if no symptoms are present, a prophylactic treatment with angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers may be considered.[46]

Occurrence of thromboembolic complications is one of the complications due to RV ventricular aneurysms or to the biventricular dilatation; long-term oral anticoagulation is indicated in the presence of documented intracavitary thrombosis, but no prophylactic antithrombotic therapy should be considered only on the basis of structural abnormalities predisposing to thrombosis.

Heart transplantation is indicated in case of refractory heart failure or of uncontrollable VT with AADs and catheter ablation.[46]

Catheter ablation

Catheter ablation is a therapeutic option reserved to ARVC patients with sustained VT. ARVC is characterized by the presence of fibro-fatty replacement that creates scar regions responsible of macro-reentry circuit: this arrhythmic substrate is suitable for mapping and ablation. The first experiences with catheter ablation of VT in ARVC, using an endocardial approach, resulted in high acute success rate followed by a high rate of recurrences (Table II).[51-62] This may be the consequence of the disease progression and ventricular scarring worsening, which lead to new reentry circuits over time.

Given the propensity of the ARVC lesion wave front to progress from the epicardium to the endocardium, the VT reentry circuit may be confined to the epicardial layer of the RV wall. This may explain the better results obtained with a combined endocardial and epicardial approach (Table II).

TABLE II.—*Major studies on catheter ablation of ventricular tachycardia in arrhythmogenic right ventricular cardiomyopathy.*

Author (year)	Patients n° (men)	Epicardial ablation	Acute success (%)	Complications	Follow-up (months)	VT recurrences (%)
Philips 2012 [51]	87 (45)	Yes	82	2 (death, MI)	88	85
Berruezo 2012 [52]	11 (9)	Yes	100	1 (tamponade)	11	9
Garcia 2009 [53]	13 (10)	Yes	92	0	18	23
Nogami 2008 [54]	18 (13)	No	72	0	61	33
Dalal, 2007 [55]	24 (11)	No	77	1 (death)	32	85
Yao 2007 [56]	32(26)	No	84	0	28	19
Satomi 2006 [57]	17 (13)	No	88	0	26	24
Verma 2005 [58]	22 (15)	No	82	1 (tamponade)	37	36
Miljoen 2005 [59]	11 (8)	No	73	0	20	45
Marchlinski 2004 [60]	19 (18)	No	74	0	27	11
Reithmann 2003 [61]	5 (3)	No	80	0	7	20
Ellison 1998 [62]	5 (4)	No	42	0	17	0

Modified from Corrado *et al.*[46]

TABLE III.—*Major studies on implantable cardioverter defibrillator in arrhythmogenic right ventricular cardiomyopathy.*

Author (year)	Patients (N.)	Study design	Follow-up (months)	Primary prevention (%)	Mortality overall (%)	Appropriate interventions (%)	Life-saving interventions (%)	Inappropriate Interventions (%)	Complications (%)
Breithardt 1994 [64]	18	SC	17±11	0	0	50	N/A	N/A	N/A
Link 1997 [65]	12	SC	22±13	0	8	67	50	33	33
Tavernier 2001 [66]	9	SC	32±24	0	0	78	44	44	N/A
Corrado 2003 [33]	132	MC	39±25	22	3	48	24	16	14
Wichter 2004 [41]	60	SC	80±43	7	13	68	40	23	45
Rougin 2004 [42]	42	MC	42±26	40	2	78	N/A	24	14
Hodgkinson 2005 [67]	48	MC	31	73	0	70[a]	30[a]	10	6
Piccini 2005 [68]	67	SC	53±11	42	9	66	21	24	21
Boriani 2007 [69]	15	SC	65±42	40	0	33	40	7	47
Corrado 2010 [35]	106	MC	58±35	100	0	24	16	19	17
Bhonsale 2011 [36]	84	SC	57±41	100	2.4	48	19	24	24
Schuler 2012 [70]	26	SC	128	4	8	46	N/A	N/A	8

MC: multicenter study; N/A: not available; SC: single-center study. Modified from Corrado *et al*.[46]

Philips *et al.*[51] reported on the efficacy of VT catheter ablation in 87 ARVC patients who underwent a total of 175 procedures. During a follow-up of 88 months, the overall freedom from VT of the 175 procedures was 47%, 21%, and 15%, at 1, 5, and 10 years, respectively; the cumulative freedom from VT following epicardial approach (64% and 45% at 1 and 5 years, respectively) was significantly longer than endocardial. The authors demonstrated that catheter ablation reduces VT recurrences in ARVC patients, with a significantly greater success rate using the epicardial approach; however, VT recurrences during follow-up remained relatively high despite a combined endocardial/epicardial ablation strategy. Of note, only 18 patients underwent a single procedure; the remaining required a mean of 2.3 procedures to achieve the reported success rates. Moreover, more than a half of patients continued to take AADs, mostly sotalol.

Bai *at al.*[63] studied prospectively 46 ARVC patients who underwent VT ablation, with the aim to evaluate the long-term efficacy using different ablation approaches, *i.e.* endocardial-alone (N.=23 patients) versus endo-epicardial ablation (N.=26 patients). During a mean follow-up of 3 years, the combined endo-epicardial approach was associated with a significantly higher long-term success rate and was more likely to result in discontinuation of AADs.

According to the 2015 International Task Force Consensus Document, catheter ablation is recommended in the presence of incessant

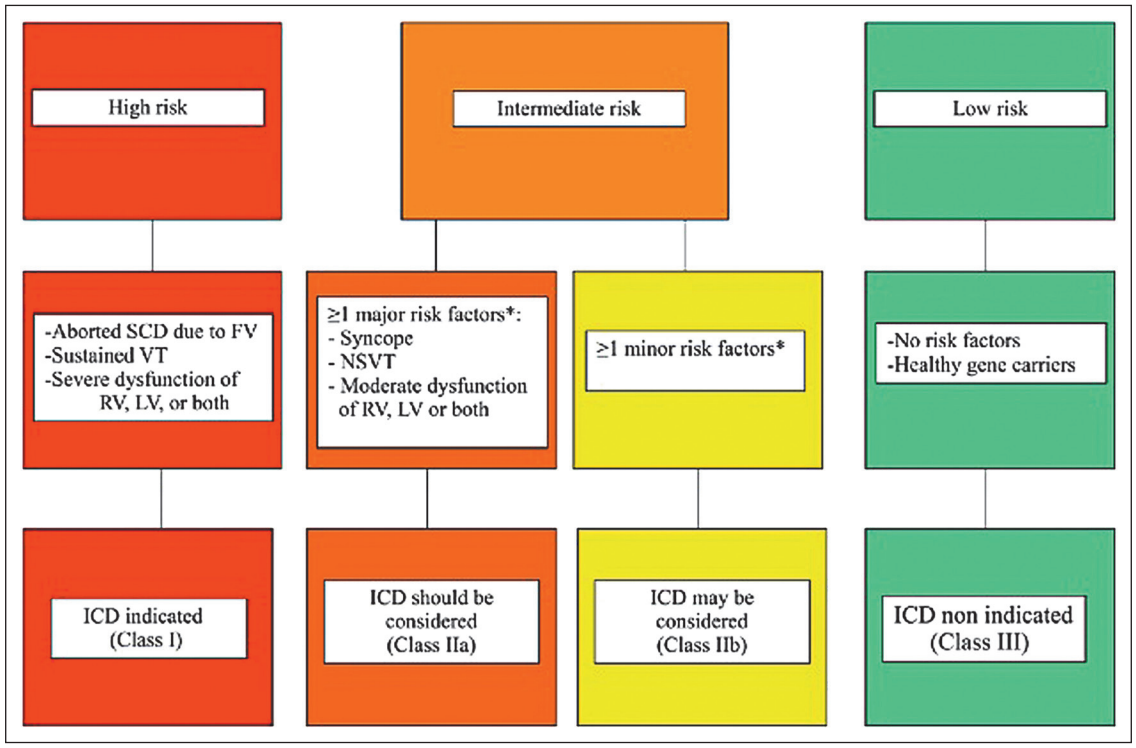

Figure 9.—Flow chart of risk stratification and indications to ICD implantation in ARVC/D.
Based on the available data on annual mortality rates associated to specific risk factors, the estimated risk of major arrhythmic events in the high-risk category is very high (10%/year); ICD implantation is mandatory for these patients. In the intermediate zone, the risk of major arrhythmic events ranges from 1 to 10%/year; indication for ICD implantation rely on the type and the number of risk factors. In the low-risk category (risk of major arrhythmic events of 1%/year), ICD is not indicated. Minor risk factors include male gender; compound and digenic heterozygosity of desmosomal-gene mutations; young age at the time of diagnosis; proband status; inducibility at programmed ventricular stimulation; amount of electroanatomic scar and electroanatomic scar-related fractionated electrograms; extent of T-wave inversion across precordial and inferior leads; low QRS amplitude and QRS fragmentation. SCD, sudden cardiac death. VF, ventricular fibrillation. VT, ventricular tachycardia. RV, right ventricle. LV, left ventricle. Modified from Corrado *et al.*[46]

VT or frequent appropriate ICD interventions, despite maximal pharmacological therapy including amiodarone. Epicardial approach is recommended after failure of endocardial ablation; an initial combined approach should be reserved to centres with experience in epicardial procedures. Finally catheter ablation may be considered as an alternative treatment to ICD therapy in selected patient with monomorphic, hemodynamically stable VT, which are refractory to pharmacological therapy.[46]

ICD therapy

Randomized trials to guide ICD therapy in ARVC patients are not available because of ethical reasons, low disease prevalence and low events rates. Data collected from observational registries demonstrated that ICD therapy is able to improve survival in ARVC patients, by interruption of potentially fatal ventricular tachyarrhythmia (Table III).[33, 35, 36, 41, 42, 64-70] On the other hand, ICD therapy is associated with an increased morbidity due to device related complications and to inappropriate ICD interventions. The meta-analysis by Schinkel [5] on the efficacy and safety of ICD therapy in ARVC patients demonstrated a very low annual cardiac mortality rate (0.9%) and an annual rate of appropriate ICD intervention of 9.5%. On the other hands, rates of complications, mostly due to lead failure or inappropriate ICD interventions, were respectively of 4.4%/year and 3.7%/year. Difficulties in ICD lead place-

ment into the RV and loss of sensing/pacing function during follow-up are both related to ARVC pathobiology, which is characterized by progressive myocardial loss and fibrofatty replacement. The incidence of inappropriate ICD discharges, mostly due to supraventricular tachyarrhythmia, can be lowered by appropriate ICD programming (71) and administration of beta-blockers. Although the use of dual-chamber detection algorithms offers the potential to reduce the number of inappropriate interventions by improving discrimination of ventricular from supraventricular arrhythmias, an additional lead in atrium predisposes to a higher incidence of early and late postoperative complications. A recent prospective single center study [72] analyzed the rate of ICD related complications among young patients with cardiomyopathies, including ARVC. During a follow-up period of more than 6 years, 27.1% of patients experienced a total of 49 adverse ICD-related events. The study results highlight the concept that the indications for ICD therapy should be the result of a balanced evaluation of the arrhythmic patients profile and the potential risk of device related complications.

According to the 2015 Consensus Statement on treatment of ARVC, 3 categories of risk can be considered (Figure 9).

Patients in the *low risk* category are probands without risk factor or healthy gene carriers, with an estimate event rate <1%/year; in this population ICD is not recommended. Because ARVC is a progressive disease, close clinical follow-up is warranted to timely identify the occurrence of new symptoms and worsening of the disease overtime. The presence of a history of aborted SCD due to VF, sustained VT or severe RV and/or LV dysfunction characterizes the high risk category of patients (event rate >10%/year), who most benefit from ICD implantation. Patients with severe RV and/or LV dysfunction are considered at high risk for SCD regardless of life-threatening ventricular arrhythmias. The management of patients with *intermediate risk* (*i.e.* patients with ≥1 risk factors and no VF or sustained VT) is challenging. In the presence of "major" risk factors (syncope, non-sustained VT or moderate ventricular dysfunction) a prophylactic ICD should be considered. Among patients with minor risk factors, the decision to implant an ICD should be made on individual basis.[46]

Conclusions

ARVC is a progressive disease characterized by the risk of ventricular arrhythmias and congestive heart failure. Mutations in the genes encoding for desmosomal proteins play a key role in the pathogenesis of fibrofatty replacement of the myocardial and the development of the disease phenotype. Affected individuals may present with SCD, but many will remain asymptomatic lifelong. Diagnostic and treatment modalities are improving, but many questions remain. Although the ICD is effective at preventing SCD, identification of appropriate ARVC candidates for ICD implantation is not always clear.

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