Arrhythmogenic Disorders of Genetic Origin

Arrhythmogenic Right Ventricular Cardiomyopathy

Cristina Basso, MD, PhD; Domenico Corrado, MD, PhD; Barbara Bauce, MD, PhD; Gaetano Thiene, MD, FRCP

Arrhythmogenic disorders of genetic origin include structural cardiomyopathies and inherited arrhythmic syndromes.1 Arrhythmogenic right ventricular cardiomyopathy (ARVC) is listed among the former, because it is characterized by structural and functional abnormalities of the right ventricle (RV), ranging from regional wall motion abnormalities and aneurysms to global dilation and dysfunction, with or without left ventricular involvement.2-4 The clinical picture is usually dominated by ventricular arrhythmias, even at risk of sudden cardiac death in young people during effort,5-7 thus justifying the adjective arrhythmogenic. However, it recently has been emphasized that in the early stages (concealed phase) the disease can resemble ion channel diseases, such as long QT and Brugada syndromes, because it can carry the risk of ventricular arrhythmias before the onset of overt structural abnormalities. Thus, early diagnosis and risk stratification pose major clinical challenges with the natural history of ARVC.

Genetic Background

ARVC is a relatively recent nosologic entity when compared with other inherited arrhythmogenic disorders, such as hypertrophic cardiomyopathy or long QT syndrome. However, after the identification of the first disease-causing gene,4 many steps forward have been made in the knowledge of its molecular background, which led to the current belief of a genetically determined cardiomyopathy.9 In the 1990s, the difficulty in determining affected members in ARVC family trees, mostly because of the variable penetrance and the low sensitivity of diagnostic criteria, represented the major obstacle for linkage analysis and candidate gene studies. The first ARVC-causing gene (ie, JUP-encoding plakophilin) was identified only in 2000 in a fully penetrant, autosomal-recessive syndrome, previously mapped on chromosome 17, and characterized by an easily recognizable cardiocutaneous phenotype, ie, the Naxos syndrome.8,10 In the same year, a recessive mutation of the gene DSP-encoding desmoplakin was found to cause a similar cardiocutaneous phenotype, ie, Carvajal syndrome, with predominant left ventricular (LV) involvement.11 Thus, the turning point for discovering the molecular basis of ARVC was represented by the investigation of cardiocutaneous syndromes.12 DSP then was the first defective gene to be identified in 2002 in autosomal-dominant ARVC.13 Soon after, other desmosomal genes have been discovered, ie, PKP2-encoding plakophilin-2, DSG2-encoding desmoglein-2, DSC2-encoding desmocollin-2, and JUP even in dominant forms.14-17 With the exception of a few other genes, such as Ryr2-encodingryanodine 2 receptor, TGF-β3-encoding transforming growth factor-β3, and TMEM43-encoding transmembrane protein 43, also known as LUMA,18-20 the most common disease genes encode desmosomal proteins (Table 1). More recently, DES-encoding desmin, TTN-encoding titin, LMNA-encoding lamin A/C, and PLN-encoding phospholamban have been suggested as novel ARVC genes, although they account for overlap syndromes characterized mostly by a dilated cardiomyopathy phenotype and a high prevalence of conduction disease.21-24

Founder mutations effects, geographic differences in either genetic or nongenetic factors, different definitions of mutation pathogenicity, and various diagnostic criteria adopted are the main factors that could explain the variable prevalence of pathogenic mutations among ARVC populations.25-32 Recent data coming from large series of familial ARVC demonstrate that up to 70% of index cases present a causal/possibly causal desmosomal gene mutation.31 The majority of mutations involve PKP2 and DSG2, followed by DSP and DCS2. Although these proportions are similar in the United Kingdom and Italy, the North America series differs in showing only 1% of DSP mutations.26 Even more different are the data coming from the Netherlands ARVC network, which identified PKP2 gene mutation, mostly represented by truncating mutations, in the majority (90%) of gene carriers.32 ARVC should not be considered just a monogenic disease, but rather a complex genetic disease, characterized by marked intrafamilial and interfamilial phenotype diversity. A significant proportion of the alleles identified are of low pathogenicity, because many family members carrying a single mutation do not meet the Task Force criteria. Compound heterozygous mutations or digenic mutations are not so rarely found27-29 as to support the concept of a gene-dose effect in determining the disease phenotype. This is quite evident in the recessive cardiocutaneous syndromes, which are characterized by an earlier clinical onset of cardiac involvement with a higher penetrance of complications than the autosomal-dominant form.33

In the clinical setting, candidates for genetic test include both ARVC index cases and family members of those
gene-positive. There is not yet a well-defined role for routine genetic screening to confirm a clinical diagnosis in index cases. Whereas a positive genotyping is supportive but not always confirmatory of ARVC diagnosis, a negative genetic test is noncontributory because 30% to 50% of ARVC probands do not carry a defective desmosomal gene. However, the identification of a rare genetic variant cannot be surely diagnostic, particularly when dealing with the most frequent situation of missense mutations. If the mutation screening yields a novel genetic variant, not previously reported as causal, then pathogenicity must be proven by traditional criteria. Of note, an overall yield of mutations in ARVC susceptibility genes has been recently demonstrated in 16% of healthy subjects compared with 58% of ARVC index cases. By considering only in-frame and frame-shift insertions and deletions, splice junction and nonsense mutations, the prevalence decreased to 0.5% in controls versus 43% in probands, suggesting that rare missense mutations should be viewed with great caution.

Cascade screening of family members remains the main current indication for genetic test in ARVC when mutation pathogenicity has been proven. In fact, it allows the early identification of asymptomatic carriers (healthy carriers) who must be considered at risk, because the disease is progressive and can appear later, due to the age-related penetrance. Frequent clinical check-ups are needed and physical activity/competitive sports should not be allowed, considering also the legal implications.

At the same time, the noncarriers, who represent ≈50% of those tested, can be considered healthy without the risk of disease transmission and do not need further check-ups. Predictive diagnosis is usually proposed in all family members of a genotyped proband after the age of 10 years. However, relatives with borderline clinical findings should not be discharged just because of a negative gene test, because the identified genetic variant in the index case may be accompanied by additional hits not yet identified. In general, genetic screening should be performed at referral clinical centers for inherited cardiovascular disorders to properly interpret test results, considering that genetic testing cannot override clinical judgment of index case and family members, and analysis of cosegregation is often crucial to determine the pathogenic significance of a mutation.

### Clinical Presentation

The most typical clinical presentation of ARVC consists of palpitations, syncope, cardiac arrest, or sudden cardiac death (SCD) in adolescents or young individuals. A predilection for the male sex (male/female ratio, 3:1) in the second to the fourth decades of life has been reported, although an equal sex distribution and late appearance in life have been noted in more recent United States series. Nonspecific clinical features, particularly in those of pediatric age, include chest pain with myocardial enzyme release in the setting of normal coronary arteries or features mimicking myocarditis or acute myocardial infarction. Ventricular tachycardia (VT) of left bundle branch block morphology is the primary reason to suspect ARVC. The presence of T-wave inversion in V1-V3 or premature ventricular complexes of left bundle branch block morphology on 12-lead ECG could be also the first alarming signs during a cardiological check-up. Less common presentation is congestive heart failure that may mimic dilated cardiomyopathy.

### Table 1. Genetics of Arrhythmogenic Right Ventricular Cardiomyopathy

<table>
<thead>
<tr>
<th>Reference</th>
<th>Chromosome</th>
<th>Gene</th>
<th>Protein</th>
<th>Mode of Inheritance</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>McKoy et al8</td>
<td>17q21</td>
<td>JUP</td>
<td>Junction plakoglobin</td>
<td>AR</td>
<td>Cardiocutaneous syndrome*</td>
</tr>
<tr>
<td>Asimaki et al17</td>
<td>17q21</td>
<td>JUP</td>
<td>Junction plakoglobin</td>
<td>AR</td>
<td>Cardiocutaneous syndrome†</td>
</tr>
<tr>
<td>Norgot et al11</td>
<td>6p24</td>
<td>DSP</td>
<td>Desmoplakin</td>
<td>AR</td>
<td></td>
</tr>
<tr>
<td>Rampazzo et al13</td>
<td>6p24</td>
<td>DSP</td>
<td>Desmoplakin</td>
<td>AR</td>
<td></td>
</tr>
<tr>
<td>Gerull et al14</td>
<td>12p11</td>
<td>PKP2</td>
<td>Plakophilin-2</td>
<td>AD, AR</td>
<td></td>
</tr>
<tr>
<td>Pilichou et al15</td>
<td>18q12</td>
<td>DSG2</td>
<td>Desmoglein-2</td>
<td>AD</td>
<td></td>
</tr>
<tr>
<td>Syrris et al19</td>
<td>18q12</td>
<td>DSC2</td>
<td>Desmocollin-2</td>
<td>AD, AR</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Extradesmosomal genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tiso et al19</td>
</tr>
<tr>
<td>Beffagna et al19</td>
</tr>
<tr>
<td>Merner et al20</td>
</tr>
<tr>
<td>van Tintelen et al21</td>
</tr>
<tr>
<td>Taylor et al22</td>
</tr>
<tr>
<td>Quarta et al23</td>
</tr>
<tr>
<td>Van der Zwaag et al24</td>
</tr>
</tbody>
</table>

ARVC indicates arrhythmogenic right ventricular cardiomyopathy; AD, autosomal-dominant; AF, atrial fibrillation; AR, autosomal recessive; CPVT, catecholaminergic polymorphic ventricular tachycardia; DC, dilated cardiomyopathy; HC, hypertrophic cardiomyopathy.

*Naxos disease.
†Carvajal disease.
Differential diagnosis include idiopathic RV outflow tachycardia, sarcoidosis, myocarditis, dilated cardiomyopathy, Chagas disease, RV infarction, and Brugada syndrome; congenital heart disease with right chamber overload, such as Ebstein anomaly, atrial septal defect, partial anomalous venous return, Uhl disease; and pulmonary hypertension, are other clinical phenocopies. In a prospective study of consecutive patients with suspected ARVC, evaluated by a standard protocol including biopsy, a surprisingly high incidence (15%) of cardiac sarcoid was found. The only clinical features discriminating between the two entities were LV dysfunction and histological findings. However, the most challenging differential diagnosis remains that with idiopathic RV outflow tachycardia, which is a benign nonfamilial condition. The absence of ECG repolarization/depolarization abnormalities and of RV structural changes as well as recording of a single VT morphology and noninducibility at programmed ventricular stimulation with a normal voltage map provide evidence for the idiopathic nature of the VT. In endurance athletes, physiologic adaptations to training can lead to RV enlargement, ECG abnormalities, and arrhythmias, reflecting the increased hemodynamic load during exercise. Global RV systolic dysfunction or regional wall motion abnormalities can point to ARVC rather than to physiologic ventricular enlargement attributable to overload. In the absence of obvious RV structural changes, the ECG changes may be considered benign, if all other noninvasive investigations have been inconclusive.

In the suspicion of ARVC, the routine diagnostic work-up consists of clinical and family history collection, physical examination, chest x-ray, 12-lead ECG, 24-hour ambulatory ECG, signal-averaged ECG, stress test, and 2-dimensional echocardiography. When noninvasive evaluation is inconclusive, patients may require further examination by contrast-enhanced cardiac magnetic resonance (CE-CMR), angiography, and endomyocardial biopsy. Follow-up assessment (every 12 months or whenever clinical symptoms develop or worsen) is conducted by serial noninvasive tests, such as ECG (both at rest and during exercise), Holter monitoring, echocardiography, and CE-CMR in selected cases.

Because there is no single criterion (gold standard) that is sufficiently specific to reach the diagnosis of ARVC, multiple categories of diagnostic information (ie, familial, electrocardiographic, arrhythmic, morphofunctional, and histopathologic) have been combined, leading to the 1994 diagnostic criteria. With time, the original criteria have been shown to lack sensitivity for identification of early or minor phenotypes, particularly in the setting of familial disease and have been shown to lack quantitative cut-off values for morphofunctional parameters, including imaging, ECG, and tissue characterization by endomyocardial biopsy. This is why the criteria have been recently revised, with the goal of improving diagnostic sensitivity but with the important requisite of maintaining diagnostic specificity. Overall, according to the revised criteria, diagnosis of ARVC is fulfilled by 2 major or 1 major and 2 minor criteria or 4 minor (definite diagnosis), by 1 major and 1 minor or 3 minor criteria (borderline diagnosis), or by 1 major or 2 minor criteria from different categories (possible diagnosis).

Traditionally, 3 clinical phases of ARVC have been identified: the subclinical phase with concealed structural abnormalities (concealed disease), even though SCD may be the first manifestation; the classical phase with palpitations, syncope, ventricular arrhythmias, and structural changes fulfilling the established diagnostic criteria (overt disease); and the advanced phase, with severe structural progression, dilatation, and systolic dysfunction that may mimic dilated cardiomyopathy (end-stage disease). However, whereas in the past LV involvement was considered an expression of the advanced disease phase, it is currently known that the disease can start with isolated or predominant LV involvement since the early stages, in the absence of systolic dysfunction.

The introduction of CMR was crucial to the study of ARVC, because of its ability to provide a noninvasive tissue characterization of the ventricular myocardium. At the beginning the attention was focused on the ability of CMR to detect fatty tissue in the RV free wall, but its limited diagnostic specificity in the absence of concomitant wall motion abnormalities and the high degree of interobserver variability became soon evident. In recent years, the advent of gadolinium enhancement technique to detect intramyocardial fibrosis was fundamental to foster the use of CE-CMR for ARVC diagnosis, because it represents a unique tool for identifying early or minor LV involvement, even in the absence of morphofunctional changes. Genotype–phenotype studies using CE-CMR demonstrated coexistence of classic RV disease with left-dominant or biventricular forms in up to two-thirds of families, supporting the adoption of the broader term arrhythmogenic cardiomyopathy.

Electroanatomic mapping is an invasive tool able to identify the abnormal low-voltage areas because of loss of electrically active myocardium (ie, electroanatomic scar) through an endocardial catheter approach. More recently, the epicardial approach confirmed the well-known pathologic concept that fibro-fatty scar is more evident on the epicardial than on the endocardial side. However, because of the invasiveness, electroanatomic mapping is performed in selected cases and mainly for differential diagnosis with idiopathic RV outflow tachycardia and to guide catheter ablation.

**Risk Stratification**

The natural history of ARVC is characterized by a spectrum of ventricular arrhythmias ranging from premature ventricular complexes to sustained VT or ventricular fibrillation (VF). Typically, ventricular arrhythmias show a left bundle branch block morphology pointing to an origin from the RV; the QRS axis usually suggests the site of origin, ie, inferior axis from the RV outflow tract and superior axis from the RV inferior wall or the apex. Patients with widespread ARVC may show several morphologies of VT.

The overall incidence of cardiac arrest attributable to VF varies among different series, ranging from a low mortality rate in familial forms during a mean follow-up of 8.5 years (0.08% per year in the series by Nava et al) to high mortality rate mostly attributable to SCD during a mean follow-up of 4.6 years (3.6% per year, in the series by Lemola et al) (Table 2).
VF is the mechanism of SCD in young people with ARVC, who are often previously asymptomatic; in this subset of patients, VF is likely related to a disease hot phase, with acute myocyte death and reactive inflammation, often characterized by dynamic T-wave inversion, ST segment elevation, and myocardial enzyme release.2,30,38 Older patients with a long-lasting disease more often experience scar-related, hemodynamically stable VT.2,3 More recently, gap junction remodeling and ion channel interference preceding the fibro-fatty scar have been postulated as alternative substrates for conduction delay and ventricular arrhythmias in the prephenotypic phase of the disease (Figure 1), as supported by experimental animal models.62–66

The unpredictability of SCD in a subgroup of patients explains why there has been a trend toward implantable cardioverter-defibrillator (ICD) placement once the disease is diagnosed, without appropriate risk stratification. Prevention of SCD is the most important management strategy of ARVC. Retrospective analysis of clinical and pathologic series identified a number of risk factors for SCD (Table 3). However, the prognostic value of these single or combined risk factors has not been prospectively evaluated and risk stratification still remains largely empiric.

Previous arrhythmic cardiac arrest and hemodynamically unstable VT have been demonstrated to be independent risk factors for life-saving ICD interventions (ie, shock on VF episodes) in a large series of ARVC patients.52 However, patients undergoing implantation because of VT without hemodynamic compromise had a better outcome, with a negligible incidence of VF during follow-up. Resuscitated VF is a malignant prognostic factor; in the series by Canu et al.,54 a history of aborted SCD from VF was documented in 2 out of 3 patients who died suddenly.

The importance of syncope as a risk factor for SCD in ARVC was first outlined by Marcus et al.52 According to the data by Turrini et al.,68 syncope is an independent predictor of SCD, with a sensitivity of 40% and a specificity of 90%. A history of syncope was ascertained in all 3 SCD victims compared with only 2 out of 12 patients who survived in the series by Blomstrom-Lundqvist et al.51 Nava et al53 confirmed that syncope was the only clinical variable significantly associated with SCD in 19 ARVC probands, whereas it was never observed among 132 living relatives. In the Darvin II multicenter study, syncope has been proven to be the strongest predictor of either any appropriate discharges or life-saving device interventions in patients with ARVC who had an ICD for primary prevention;79 in particular, the 9% annual incidence of shocks on VF among patients with previous syncope is comparable with that observed in patients with a history of cardiac arrest or sustained VT. Apparently, contrast data come from a more recent study of prophylactic ICD for primary prevention performed in the Johns Hopkins ARVC cohort,70 in which a history of syncope was less often present than in the Darvin study (27% versus 39%) and the majority of patients (75%) receiving any appropriate ICD therapy did not have a history of syncope. However, also in the Johns Hopkins ARVC cohort, nearly one-half of patients with syncope experienced appropriate ICD therapy at a comparably high rate (9% per year). Importantly, significantly more patients with recent unexplained syncope (<6 months before ICD) experienced ICD interventions than those with remote syncope, suggesting that a history of recent syncope is at higher risk of ventricular arrhythmias and should prompt consideration for ICD therapy.

These data support the concept that, with a difference from other genetic cardiomyopathies and channelopathies in which syncope can be vaso-vagal or nonarrhythmic in origin, most syncope-related episodes in ARVC are attributable to ventricular arrhythmias and are associated with a poor prognosis, similar to sustained VT or VF.

### Table 2. Annual Mortality Rate, Heart Failure, and Sudden Cardiac Death in Arrhythmogenic Right Ventricular Cardiomyopathy Series

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Patients</th>
<th>Follow-up (y)</th>
<th>ARVC-Related Death (n) and Annual Mortality Rate (%)</th>
<th>HF Death</th>
<th>SC Death</th>
<th>Heart Transplantation (%)</th>
<th>ICD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blomstrom et al</td>
<td>1987</td>
<td>15</td>
<td>8.8</td>
<td>3 (2.3)</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Marcus et al</td>
<td>1989</td>
<td>33</td>
<td>5.9</td>
<td>5 (2.6)</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Leclerq and Coumel</td>
<td>1989</td>
<td>58</td>
<td>8.8</td>
<td>4 (0.8)</td>
<td>3</td>
<td>1</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Canu et al</td>
<td>1993</td>
<td>22</td>
<td>10.7</td>
<td>3 (1.2)</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Kullo et al</td>
<td>1995</td>
<td>20</td>
<td>7</td>
<td>3 (2)</td>
<td>1</td>
<td>2</td>
<td>2 (10)</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Nava et al</td>
<td>2000</td>
<td>132</td>
<td>8.5</td>
<td>1 (0.08)</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2 (1.5)</td>
</tr>
<tr>
<td>Protonotarios et al</td>
<td>2001</td>
<td>26*</td>
<td>10</td>
<td>8 (3)</td>
<td>2</td>
<td>6</td>
<td>0</td>
<td>3 (11.5)</td>
</tr>
<tr>
<td>Hulot et al</td>
<td>2004</td>
<td>130</td>
<td>8.1</td>
<td>21 (2.0)</td>
<td>14</td>
<td>7</td>
<td>0</td>
<td>10 (7.7)</td>
</tr>
<tr>
<td>Dalal et al</td>
<td>2005</td>
<td>69</td>
<td>6</td>
<td>3 (0.7)</td>
<td>1</td>
<td>2</td>
<td>2 (3)</td>
<td>47 (68)</td>
</tr>
<tr>
<td>Lemola et al</td>
<td>2005</td>
<td>61</td>
<td>4.6</td>
<td>10 (3.6)</td>
<td>2</td>
<td>8</td>
<td>5 (8)</td>
<td>24 (39)</td>
</tr>
<tr>
<td>Peters et al</td>
<td>2007</td>
<td>313</td>
<td>8.5</td>
<td>9 (0.3)</td>
<td>4</td>
<td>5</td>
<td>2 (0.6)</td>
<td>35 (11)</td>
</tr>
<tr>
<td>Watkins et al</td>
<td>2009</td>
<td>50</td>
<td>4.5†</td>
<td>9 (2.8)</td>
<td>3</td>
<td>6</td>
<td>NR</td>
<td>20 (40%)</td>
</tr>
<tr>
<td>Pinamonti et al</td>
<td>2011</td>
<td>96</td>
<td>10.7</td>
<td>12 (1.2)</td>
<td>6</td>
<td>6</td>
<td>7 (7.3)</td>
<td>12 (12.5)</td>
</tr>
<tr>
<td>Li et al</td>
<td>2012</td>
<td>30</td>
<td>5.6</td>
<td>1 (0.6)</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>13 (43.3)</td>
</tr>
</tbody>
</table>

†Homozygous carriers.

HF indicates heart failure; NR, not reported; and SC, sudden cardiac.
Among electrocardiographic parameters, right precordial QRS prolongation, QRS dispersion, and late potentials on signal-averaged ECG have been associated with an increased arrhythmic risk in ARVC. Right precordial QRS prolongation correlates with the arrhythmic risk as demonstrated by Turrini et al, because patients who died suddenly showed a QRS prolongation in V1-V2/V3 compared with living ARVC patients with or without VT (QRS duration 125 ms versus 113 ms and 106 ms, respectively). Accordingly, Nasir et al noted that a prolonged right precordial QRS complex with a pattern of delayed S-wave upstroke ≥55 ms is a significant predictor of severity and VT inducibility by programmed ventricular stimulation (PVS). Moreover, a QRS dispersion >40 ms was the strongest independent predictor of SCD in the ARVC series by Turrini et al, with a sensitivity of 90% and a specificity of 77%. On the contrary, there are no data supporting a role of signal-averaged ECG for arrhythmic risk stratification in ARVC. In particular, late potentials were not predictive of ventricular arrhythmias in the series by Blomström-Lundqvist et al and Leclercq and Coumel, because the prevalence of late potentials was similar in patients with or without sustained VT and their absence did not exclude the risk of SCD. In the study by Turrini et al, although late potentials were univariate predictors of sustained VT, the only independent predictor of arrhythmic events at multivariate analysis remained a decreased RV ejection fraction.

RV dilatation/dysfunction and LV involvement are well-established clinical markers of a worse prognosis in ARVC. In the study by Hulot et al of the long-term follow-up of 130 patients with ARVC, right heart failure and LV dysfunction were independent risk factors predicting cardiovascular death. Similar data were found by Peters et al in 121 ARVC patients, in whom advanced RV dilatation/dysfunction and LV involvement were major clinical variables associated with an increased risk of SCD. Turrini et al reported a significant association between a reduced RV ejection fraction (≤50%) and sustained ventricular arrhythmias. Extensive RV dysfunction was an independent risk factor for appropriate device discharges in ICD studies. Prospective studies will clarify whether LV involvement in terms of tissue characterization by CE-CMR, even preceding LV dilatation/dysfunction, is an independent risk factor for SCD.

The available data do not support the routine use of PVS for risk stratification in ARVC, because of a low predictive accuracy. These data are in agreement with the limitation of electrophysiological study for arrhythmic risk stratification of other nonischemic heart disease, such as hypertrophic and dilated cardiomyopathy. Both DARVIN studies demonstrated that the incidence of appropriate and life-saving ICD discharges did not differ among patients who were and were not inducible at PVS, regardless of their indication for ICD implant. In the study by Wichter et al, inducibility of VT or VF at preimplant PVS in ARVC patients with history of cardiac arrest or sustained VT demonstrated just a trend toward statistical significance for appropriate ICD interventions. In the recent Johns Hopkins series, inducibility at PVS was a significant predictor of any appropriate ICD therapy for primary prevention in ARVC patients. However, the positive and negative predictive values of PVS inducibility were 65% and 75%, respectively, and a sizeable proportion of patients experienced ICD interventions over the follow-up despite a negative test. A higher event rate among this single-center study population as well as the population characteristics unique to each series could explain this difference with the Darvin II data. Of note, the role of PVS inducibility as either univariate or multivariate predictors of life-saving ICD discharges on VF was not demonstrated in the Johns Hopkins series.

Although electroanatomic voltage mapping can enhance diagnostic accuracy for ARVC, its value for risk stratification of SCD remains to be investigated. Preliminary data of our group show a significant correlation between the presence and extent of RV electroanatomic scars and the incidence of malignant arrhythmic events during follow-up, such as SCD, cardiac arrest attributable to VF, appropriate ICD intervention, and syncopal VT. Other authors suggest that the

Table 3. Risk Factors for Sudden Death in Arrhythmogenic Right Ventricular Cardiomyopathy

<table>
<thead>
<tr>
<th>Strongest risk factors</th>
</tr>
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<tbody>
<tr>
<td>Prior cardiac arrest/VF</td>
</tr>
<tr>
<td>Fast/poorly tolerated sustained VT</td>
</tr>
<tr>
<td>Unexplained syncope</td>
</tr>
<tr>
<td>Other recognized risk factors</td>
</tr>
<tr>
<td>Young age at diagnosis</td>
</tr>
<tr>
<td>Hemodynamically stable sustained VT</td>
</tr>
<tr>
<td>Nonsustained VT</td>
</tr>
<tr>
<td>Severe RV dysfunction</td>
</tr>
<tr>
<td>LV involvement</td>
</tr>
<tr>
<td>Questionable risk factors</td>
</tr>
<tr>
<td>Family history of SCD</td>
</tr>
<tr>
<td>QRS dispersion/delayed S-wave upstroke in V1-V2</td>
</tr>
<tr>
<td>Inducibility at programmed ventricular stimulation</td>
</tr>
<tr>
<td>Electroanatomic scar (by voltage mapping)</td>
</tr>
<tr>
<td>Molecular genetics</td>
</tr>
<tr>
<td>Proband status</td>
</tr>
<tr>
<td>Premature ventricular complex count at Holter &gt;1000/24 h</td>
</tr>
</tbody>
</table>

ICD indicates implantable cardioverter-defibrillator; LV, left ventricular; RV, right ventricular; SCD, sudden cardiac death; VT, ventricular tachycardia.
presence of fragmented and delayed electrograms within the electroanatomic scars, regardless of their extension, predicts arrhythmic events in ARVC patients.77

Published studies on ICD in ARVC, for either secondary or primary prevention of SCD, provide useful insights for therapy-based risk stratification. DARVIN I study67 yielded the following predictors of appropriate ICD interventions: previous cardiac arrest; VT with hemodynamic compromise; LV involvement; and younger age. A long-term follow-up study of patients with Naxos disease confirmed that arrhythmic syncpe, LV involvement, early onset of symptoms, and structural progression were the stronger predictors of SCD.56

Whereas there is general agreement that survivors of an episode of VF or sustained VT benefit best from ICD because of the high incidence of malignant arrhythmia recurrences67 (Figure 2), the role of prophylactic ICD in ARVC patients with no history of sustained tachyarrhythmias or cardiac arrest is less clear.69 In the DARVIN II study, patients who received an ICD because of a previous syncope had a similar incidence of appropriate life-saving interventions triggered by either VF or ventricular flutter as did patients with a history of aborted SCD/poorly tolerated sustained VT (Figures 3 and 4). However, asymptomatic patients had a favorable long-term outcome, regardless of familial SCD and electrophysiologic study findings. Finally, demonstration of nonsustained VT on 24-hour Holter monitoring or exercise testing in asymptomatic patients confers an increased risk of development of VT during the follow-up, although it did not significantly predict the occurrence of potentially lethal VF/ventricular flutter.69

More recently, the John Hopkins series identified clinical variables such as inducibility at PVS, the presence of nonsustained VT, proband status, and Holter monitoring premature ventricular complexes >1000/24 hours as significant predictors of any appropriate ICD therapy, although their value for predicting life-saving ICD interventions on VF was not shown.70 Moreover, the presence of multiple risk factors incrementally increased the likelihood of appropriate ICD therapy with mutation status and electrocardiographic and major structural abnormalities not affecting this risk. Patients, especially family members with none of these markers, appear to be at low risk for life-threatening ventricular arrhythmias.

Sports activity has been shown to increase the risk of SCD by 5-fold in people affected by ARVC78 (Figure 5), because acute volume overload with RV stretching during effort and sympathetic stimulation are major triggers of life-threatening ventricular arrhythmias.79,80 Additionally, mechanical stress may promote the underlying myocardial substrate accelerating disease progression. This explains why sport preparticipation screening with early detection of asymptomatic ARVC patients is life-saving. The decline of SCD, from 3.8 per 100 000 to 0.4 per 100 000 per year after the implementation of the systematic screening in Northeast of Italy, was mostly attributable to disqualification of young competitive athletes affected by cardiomyopathies, ARVC included.7 Of note, there are experimental data of a training-dependent development of ARVC in plakoglobin-deficient mice.81 Accordingly, drugs such as beta-blockers or even angiotensin-converting enzyme inhibitors might prevent the progression of disease; however, this is speculative and remains to be proven in asymptomatic or borderline ARVC patients and gene carriers.82

For similar reasons, the cardiovascular system adaptation to increased plasma volume and cardiac output observed during pregnancy also could have an impact on ARVC progression.83 A careful clinical follow-up of women, particularly in the last trimester of pregnancy and puerperium, is recommended because of an increased risk of ventricular arrhythmias.

Finally, current data are too limited to allow speculation of the potential role of genotyping for risk stratification and therapy in ARVC.2,3,34,35 With the exception of the very malignant
variant of ARVC attributable to TMEM43 gene mutation,\textsuperscript{84} genotype–phenotype correlations in desmosomal ARVC have failed to identify so-called malignant mutations to require prophylactic ICD therapy. No significant differences have been reported with regard to a series of clinical, ECG, and arrhythmic variables between ARVC mutation carriers and noncarriers. In addition, the proportion of patients who received an ICD and the incidence of appropriate discharges during the follow-up did not differ between gene-positive and gene-negative probands. Additional environmental or genetic factors, such as the presence of genetic modifiers or compound heterozygous mutations, may influence the severity of disease clinical expression.

**Current Management**

Besides lifestyle advice, therapeutic options in ARVC include antiarrhythmic drug therapy, catheter ablation, and the ICD.\textsuperscript{2,3,85,86} Anti-arrhythmic drug therapy is used to reduce or prevent arrhythmias and, among patients with an ICD, to reduce both appropriate and inappropriate ICD interventions. Prospective and randomized studies of antiarrhythmic drugs in ARVC are not available and most data still refer to retrospective analysis in single centers with limited study populations.

The largest experience of pharmacologic therapy in ARVC comes from Germany, with 191 patients and 608 drug tests.\textsuperscript{85,87} Sotalol at a dosage of 320 to 480 mg per day was the most
effective drug, with an a 68% overall acute efficacy rate. In a small subset of patients with nonreentrant VT and possible triggered activity or autonomic abnormal automaticity, verapamil and beta-blockers had efficacy rates of 44% and 25%. Amiodarone alone or in combination with beta-blockers also was effective, whereas class I antiarrhythmic drugs were only effective in a minority of patients (18%). In the long-term, sotalol or nonpharmacologic treatments are preferentially effective in a minority of patients (18%).

Amiodarone alone or in combination with beta-blockers had efficacy rates of 44% and 25%. Amiodarone alone or in combination with beta-blockers had efficacy rates of 44% and 25%. Amiodarone alone or in combination with beta-blockers had efficacy rates of 44% and 25%. Amiodarone alone or in combination with beta-blockers had efficacy rates of 44% and 25%. Amiodarone alone or in combination with beta-blockers had efficacy rates of 44% and 25%. Amiodarone alone or in combination with beta-blockers had efficacy rates of 44% and 25%. Amiodarone alone or in combination with beta-blockers had efficacy rates of 44% and 25%. Amiodarone alone or in combination with beta-blockers had efficacy rates of 44% and 25%. Amiodarone alone or in combination with beta-blockers had efficacy rates of 44% and 25%

Adequate monitoring of drug efficacy is fundamental in ARVC. In the experience of Wichter et al, a better long-term outcome was obtained by serial electrophysiological study (inducible VT) or Holter monitoring combined with exercise testing (noninducible VT) when compared with empirical drug treatment. The arrhythmia recurrence rate was low in patients treated with a drug that has been proven effective, whereas SCD and VT recurrences mostly occurred in patients with insufficient suppression of arrhythmias at discharge or those with inappropriate dosage of the tested antiarrhythmic drug.

The next largest study comes from the North American Registry, in which 108 patients were prospectively collected and administered an antiarrhythmic drug at the discretion of the treating physician. Note-worthy, 95 had ICD and the majority (61%) were treated with beta-blockers, including atenolol, metoprolol, bisoprolol, and carvedilol. The authors did not observe a clinical significant benefit to prevent VT or VF with beta-blockers, as compared with patients not using antiarrhythmic drugs or beta-blockers, although a trend in reduction on ICD shocks was noted.

Catheter ablation is currently indicated in patients with drug-refractory incessant VT, or with frequent VT after ICD implantation, or with single morphology of spontaneous and induced VT attributable to localized ARVC. The results of catheter ablation of ARVC-related VT vary considerably among the several single-center studies, mostly reflecting different procedural strategies and mapping techniques. A palliative rather than a curative role for catheter ablation in ARVC has been supported because of several reasons, including the progressive nature of the disease, multiple localizations (RV and LV), and multiple morphologies of VT. For instance, short-term success was achieved in 82% of patients in the series by Verma et al. However, VT recurred after 1, 2, and 3 years of follow-up in 23%, 27%, and 47% of cases, respectively. In the Dalal et al series, 85% of radiofrequency ablation procedures were followed by recurrence; the cumulative VT recurrence-free survival was 75%, 50%, and 25% after 1.5, 5, and 14 months, respectively. These data explain why catheter ablation is mostly used to reduce the frequency of VT episodes as palliative procedure.

Noteworthy, recent studies with an endo-epicardial–based ablation strategy achieved higher long-term freedom from recurrence,50,91 with no VT recurrence after 18±13 months in 77% of treated patients in the Marchlinski’s series. More recently, Philips et al, by reporting the outcome of catheter ablation of VT in 87 ARVC patients, demonstrated that despite the better results with the epicardial approach and the use of 3-dimensional electroanatomic mapping, recurrence rates remain considerable; a cumulative freedom from VT after epicardial ablation of 64% and 45% at 1 and 5 years was found, which was significantly longer than with the endocardial approach (P=0.02).92

It is widely accepted that ICD therapy improves long-term prognosis and survival in ARVC patients at high risk for SCD67,69,70,75,76,84,86–96 (Table 4). However, the significant rate of inappropriate interventions and complications as well as the psychological repercussions mostly in the younger age group strongly suggest the need to accurately stratify the individual arrhythmic risk before device implantation.97 The current threshold for ICD implantation indication differs in Europe and in the United States, being much higher in the former. Caution is particularly needed in patients with misdiagnoses of ARVC mostly based on cardiac imaging/CMR features and, in fact, do not have the disease.98

Figure 6 shows the pyramid of arrhythmic risk stratification and the current indications to ICD in ARVC patients based on the annual rate of appropriate ICD interventions against life-threatening ventricular arrhythmias (ie, episodes of VF) derived from observational studies.3 The best candidates for ICD therapy are patients with previous cardiac arrest and those with hemodynamically unstable VT (ie, associated with syncope or shock) and patients with syncope that remains unexplained after exclusion of noncardiac causes and vasovagal mechanisms. In this high-risk group of patients, the rate of appropriate ICD intervention against life-threatening ventricular tachyarrhythmias is 8% to 10% per year and the estimated mortality reduction at 36 months of follow-up ranges from 24% to 35%.99
On the contrary, ICD implantation for primary prevention in the general ARVC population seems to be unjustified. As indicated by DARVIN II study on prophylactic device implantation in ARVC patients with no sustained VT or VF, asymptomatic probands and relatives do not benefit from ICD therapy, regardless of familial SCD or inducibility at PVS.69 This patient cohort has a low arrhythmic risk over a long-term follow-up (ICD intervention rate <1 per year) and a significant rate of device-related complications and inappropriate discharges.

Patients with well-tolerated sustained VT or nonsustained VT on Holter or exercise testing have an intermediate arrhythmic risk (ICD intervention rate $\approx 1\%–2\%$ per year). In this patient subgroup, the decision for ICD implantation needs to be individualized; antiarrhythmic drug therapy (including beta-blockers) or catheter ablation seems to be a reasonable first-line therapy. Whether in the absence of syncope or significant ventricular arrhythmias, severe dilatation or dysfunction of RV, LV, or both, as well as early-onset structurally severe disease require prophylactic ICD, remain to be established. It is also a matter of debate whether the decision to implant an ICD should take into account risk factors such as the presence of premature ventricular complexes >1000/24 hours or nonsustained VT, proband status, and inducibility at PVS, either alone or in combination, which have been associated with an increased risk of any appropriate ICD intervention (mostly non–life-threatening VT) but have not been proven to significantly predict life-saving device shocks against VF.70

The incidence of heart failure and heart failure death in ARVC is quite variable in the published series (Table 2), mostly depending on the selection criteria of patients, whether referred for arrhythmias or heart failure. Treatment consists of diuretics, angiotensin-converting enzyme inhibitors and digitalis, as well as anticoagulants.2,3 In the retrospective study by Wlodarska et al99 of 126 ARVC patients followed-up for a mean period of 99±64 months, the annual incidence of thromboembolism was 0.5%. It is still debated whether prophylactic anticoagulation is needed in patients with RV aneurysms and with the left-dominant and biventricular subtypes of ARVC. Heart transplantation is the final therapeutic option in case of refractory congestive heart failure or untreatable ventricular arrhythmias with incessant electric storms.100 Left cardiac sympathetic denervation, which

### Table 4. Major Series of Implantable Cardioverter Defibrillator in Arrhythmogenic Right Ventricular Cardiomyopathy

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Patients</th>
<th>Study Design</th>
<th>Men (%)</th>
<th>Follow-up (mo)</th>
<th>Primary Prevention (%)</th>
<th>Mortality Overall (%)</th>
<th>Appropriate ICD Therapy (%)</th>
<th>Life-Saving ICD Therapy (%)</th>
<th>Complications (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breithardt et al94</td>
<td>1994</td>
<td>18</td>
<td>SC</td>
<td>72</td>
<td>17±11</td>
<td>0</td>
<td>0</td>
<td>59</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Link et al95</td>
<td>1997</td>
<td>12</td>
<td>SC</td>
<td>58</td>
<td>22±13</td>
<td>0</td>
<td>8</td>
<td>67</td>
<td>50</td>
<td>33</td>
</tr>
<tr>
<td>Tavernier et al92</td>
<td>2001</td>
<td>9</td>
<td>SC</td>
<td>89</td>
<td>32±24</td>
<td>0</td>
<td>0</td>
<td>78</td>
<td>44</td>
<td>NR</td>
</tr>
<tr>
<td>Corrado et al67</td>
<td>2003</td>
<td>132</td>
<td>MC</td>
<td>70</td>
<td>39±25</td>
<td>22</td>
<td>3</td>
<td>48</td>
<td>24</td>
<td>14</td>
</tr>
<tr>
<td>Wichter et al83</td>
<td>2004</td>
<td>60</td>
<td>SC</td>
<td>82</td>
<td>80±43</td>
<td>7</td>
<td>13</td>
<td>68</td>
<td>40</td>
<td>45</td>
</tr>
<tr>
<td>Rougin et al84</td>
<td>2004</td>
<td>42</td>
<td>MC</td>
<td>52</td>
<td>42±26</td>
<td>40</td>
<td>2</td>
<td>78</td>
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<tr>
<td>Hodgkinson et al84</td>
<td>2005</td>
<td>48</td>
<td>MC</td>
<td>63</td>
<td>31</td>
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<td>70</td>
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<tr>
<td>Corrado et al85</td>
<td>2010</td>
<td>106</td>
<td>MC</td>
<td>70</td>
<td>39±25</td>
<td>100</td>
<td>0</td>
<td>24</td>
<td>17</td>
<td>19</td>
</tr>
<tr>
<td>Bhonsale et al95</td>
<td>2011</td>
<td>84</td>
<td>SC</td>
<td>46</td>
<td>57±41</td>
<td>100</td>
<td>2.4</td>
<td>48</td>
<td>19</td>
<td>24</td>
</tr>
<tr>
<td>Schuler et al96</td>
<td>2012</td>
<td>26</td>
<td>SC</td>
<td>81</td>
<td>128</td>
<td>4</td>
<td>8</td>
<td>46</td>
<td>NR</td>
<td>8</td>
</tr>
</tbody>
</table>

ICD indicates implantable cardioverter-defibrillator; MC, multicenter; NR, not reported; SC, single center.
is a safe and effective antibrillatory therapeutic option for channelopathies,\textsuperscript{101} has been recently suggested as a potential adjuvant treatment in patients with cardiomyopathies and malignant ventricular arrhythmias, which may be exacerbated specifically by sympathetic activation.\textsuperscript{102}

**Next Steps**

The hot issues are represented by the diagnostic and prognostic role of genetics, the search for exogenous/endogenous factors modulating disease phenotype, the identification of novel disease biomarkers, the need of diagnostic criteria to identify isolated or predominant LV forms, and the development of a prospectively validated therapeutic algorithm by updating SCD risk predictors.

The original idea of a monogenic disease has evolved over the past decade into the current concept of the complex genetic disease characterized by marked intrafamilial and interfamilial phenotype diversity. There is emerging evidence that a gene–dose effect (>1 hit) may be required for clinical disease expression. Modifiers genes and additional unknown disease causing genes are currently undergoing investigation,\textsuperscript{103} facilitated by the advent of next-generation sequencing techniques.

In addition to the genetic background, other exogenous and endogenous factors (such as age, sex, strenuous exercise, drugs, hormones, infection or inflammation, and emotional stress) could modulate the disease phenotype and trigger disease progression, thus precipitating electrical instability.\textsuperscript{103,104} Currently available and developing experimental ARVC animal models represent a potential valuable resource to answer to these questions.\textsuperscript{81,105–111} For instance, in the heterozygous JUP-deficient (+/−) mice the cardiac phenotype was exacerbated by daily swimming, supporting the knowledge that endurance training could accelerate disease progression among individuals with ARVC.\textsuperscript{83} Furthermore, a load-reducing therapy (furosemide and nitrates) prevented training-induced development of ARVC in the same mouse model.\textsuperscript{111} If confirmed in large cohorts of patients, then these data could support the use of drugs such as beta-blockers and angiotensin-converting enzyme inhibitors to prevent the disease progression in borderline or healthy gene mutation carriers. Recently, the generation of patient-specific induced pluripotent stem cell–derived cardiomyocytes has been demonstrated feasible as a cellular model of ARVC,\textsuperscript{112} offering a unique platform for further understanding of the disease pathogenesis and for therapeutic applications. Effective treatment is based on the discovery of the molecular mechanisms that are involved in the disease etiology and pathogenesis.\textsuperscript{113,114}

Besides tissue biomarkers that arise early in the disease process, consisting of diminished immunoreactive signal for plakoglobin at intercalated disks,\textsuperscript{115} the role of blood biomarkers, such as circulating proinflammatory cytokines, markers of fibrosis, and many others accompanying the onset and the clinical phases of disease progression, needs to be explored. Whereas LV involvement has been considered for a long time as an expression of the advanced disease phase, it is currently well-accepted that ARVC can start with isolated or predominant LV involvement since the early stages.\textsuperscript{38,48,116,117}

Diagnostic criteria are needed to properly and timely identify these patients to better-characterize this new cohort of ARVC patients, because current clinical data are almost exclusively derived from series of ARVC patients with the classic RV-dominant disease variant. The systematic use of CE-CMR in prospective studies of familial ARVC is crucial to this aim.

The main clinical challenge remains the development of a prospectively validated risk stratification algorithm for ARVC, including the full disease spectrum. As far as the pathophysiology of ventricular arrhythmias is concerned, a new perspective is that suggesting that impaired mechanical coupling attributable to desmosomal gene mutations might account for abnormal electrical coupling or ion channel dysfunction, leading to electrical instability even before ventricular structural remodeling.\textsuperscript{62–66} If proven, then this revolutionary theory could dramatically change our approach in risk stratification and management of patients affected with ARVC.

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**References**


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