Arrhythmogenic Right Ventricular Cardiomyopathy

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

1. Genetic background

ARVC is a relatively recent nosologic entity when compared to other inherited arrhythmogenic disorders, such as hypertrophic cardiomyopathy or long QT syndrome. However, after the identification of the first disease causing gene (8), 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 90’s, the difficulty in determining affected members in ARVC family trees, mostly due to 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 (i.e. JUP-encoding plakoglobin) was identified only in 2000 in a fully penetrant, autosomal recessive syndrome, previously mapped on chromosome 17 and characterized by a easily recognizable
cardio-cutaneous phenotype, i.e. the Naxos syndrome (8,10). In the same year, a recessive mutation of DSP-encoding desmoplakin was found to cause a similar cardiocutaneous syndrome, i.e. Carvajal disease, with predominant LV involvement (11). Thus, the turning point for discovering the molecular basis of ARVC was represented by the investigation of cardio-cutaneous syndromes (12). DSP was thus the first defective gene to be identified in 2002 in autosomal dominant ARVC (13). Soon after, other desmosomal genes have been discovered, i.e. PKP2-encoding plakophilin-2, DSG2-encoding desmoglein-2 and DSC2-encoding desmocollin-2 and JUP even in dominant forms (14-17). With the exception of other few genes, such as Ryr2-encoding ryanodine 2 receptor, TGF β3-encoding the transforming growth factor β3 and TMEM43-encoding transmembrane protein 43 (18-20), the most common disease-genes encode desmosomal proteins (Table 1). More recently, the DES-encoding desmin and the TTN-encoding titin 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, respectively (21, 22).

Founder mutations effects, geographic differences in either genetic or non genetic factors, different definitions of mutation pathogenicity, and various diagnostic criteria adopted are the main factors that could explain the variable prevalence of pathogenetic mutations among various ARVC populations (23-30). Recent data coming from large series of familial ARVC are currently demonstrating that up to 70% of index cases present a causal/possibly causal desmosomal gene mutation (29). The majority of mutations involve PKP2 and DSG2, followed by DSP and DCS2. Although these proportions are similar in UK and Italy, the North America series differs in showing only 1% of DSP mutations (24). 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 (30).

ARVC should not be considered just a “monogenic” but a complex genetic disease, characterized by marked intra- and inter-familial phenotype diversity. A significant proportion of the alleles identified are of low pathogenicity, since many family members carrying a single mutation do not meet the Task Force criteria. Compound heterozygous mutations or digenic mutations are no so rarely found (25-27), as to support the concept of a gene-dose effect in determining the disease phenotype. This is quite evident in the recessive cardio-cutaneous syndromes, which are characterized by an earlier clinical onset of cardiac involvement with a higher penetrance of complications than the autosomal dominant form (31).

In the clinical setting, candidates for genetic screening include both index cases and family members of gene-positive ARVC probands. There is no yet a well-defined role for routine genetic screening to confirm a clinical diagnosis in index cases. While a positive genotyping is supportive but not always confirmatory of ARVC diagnosis, a negative genetic screening is non-contributory since 30-50% of ARVC probands do not carry a defective desmosomal gene. On the other hand, the identification of a rare genetic variant cannot be surely diagnostic, particularly when dealing with the most frequent situation of missense mutations (2,32-34). If the mutation screening yields a novel genetic variant, not previously reported as causal, 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 vs. 58% of ARVC index cases (2,34). By considering only in-frame and frame-shift insertions and deletions, splice junction and non-sense mutations, the prevalence dropped to 0.5% in controls vs. 43% in probands, as to suggest that rare missense mutations should be viewed with great caution.
Cascade genetic screening of family members remains the main current indication in ARVC, when mutation pathogenicity has been proven (2,32,33). In fact, it allows the early identification of asymptomatic carriers (“healthy carriers”) who must be considered at risk, since the disease is progressive and can appear later on, due to age-related penetrance. Frequent clinical checkups are needed and physical activity/competitive sports should not be allowed, also considering the legal implications.

At the same time, the non-carriers, who represent about 50% of those tested, can be considered healthy without the risk of disease transmission and do not need further check-up. Predictive diagnosis is usually proposed in all family members of a genotyped proband after the age of 10 years (2,32,33). However, relatives with borderline clinical findings should not be discharged just because of a negative gene test, since 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 co-segregation is often crucial to determine the pathogenic significance of a mutation.

2. Clinical presentation

The most typical clinical presentation of ARVC consists of palpitations, syncope, cardiac arrest or SCD in adolescents or young individuals. A predilection for the male gender (male/female ratio 3:1) in the second to the fourth decade of life has been reported (2,3), although an equal gender distribution and late appearance in life has been noted in more recent US series (35). Non-specific clinical features, particularly in the paediatric age, include chest pain with myocardial enzymes release in the setting of normal coronary arteries or to mimic myocarditis or
acute myocardial infarction (28,36). Ventricular tachycardia (VT) of left bundle branch block
(LBBB) morphology is the primary reason to suspect ARVC. The presence of T wave inversion
in V₁-V₃ or premature ventricular complexes (PVCs) of LBBB morphology on 12 lead ECG are
also the first alarming signs during a cardiological check-up. Less common presentation is
congestive heart failure that may mimic dilated cardiomyopathy.

Differential diagnosis include idiopathic RV outflow tachycardia, sarcoidosis,
myocarditis, dilated cardiomyopathy, Chagas disease, RV infarction, Brugada syndrome;
congenital heart disease with right chamber overload, such as Ebstein anomaly, atrial septal
defect, partial anomalous venous return, Uhl’s disease, and pulmonary hypertension, are other
clinical phenocopies (2,3). Noteworthy, 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 (37); the only clinical features discriminating
between the two entities were left ventricular dysfunction and histological findings. However,
the most challenging differential diagnosis remains that with idiopathic RV outflow tachycardia,
which is a benign non-familial condition. The absence of ECG repolarization/depolarization
abnormalities and of RV structural changes, as well as recording of a single VT morphology and
non-inducibility at programmed ventricular stimulation with a normal voltage map provide
evidence for the idiopathic nature of the VT (38). In endurance athletes, physiologic adaptations
to training can lead to RV enlargement, ECG abnormalities and arrhythmias, reflecting the
increased hemodynamic load during exercise (39). Global RV systolic dysfunction and/or
regional wall motion abnormalities can point to ARVC rather than to physiologic ventricular
enlargement due to overload. In the absence of obvious RV structural changes, the ECG changes
may be considered benign, if all other non-invasive investigations have been inconclusive.
In the suspicion of ARVC, the routine clinical work-up consists of clinical and family history collection, physical examination, chest X-ray, 12-lead electrocardiogram (ECG), 24-hour ambulatory ECG, signal-averaged ECG, stress test and two-dimensional echocardiography (2,3,40). When non-invasive 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 non-invasive tests, such as ECG, both at rest and during exercise, Holter monitoring, echocardiography and CE-CMR in selected cases.

Since there is no single criterion (“gold standard”) that is sufficiently specific to reach the diagnosis of ARVC, multiple categories of diagnostic information (i.e. familial, electrocardiographic, arrhythmic, morpho-functional, and histopathologic) have been combined leading to the 1994 diagnostic criteria (41). With time, the original criteria have been shown to lack sensitivity for identification of early/minor phenotypes, particularly in the setting of familial disease and to lack quantitative cut-off values for morpho-functional 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 (42). 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); 1 major and 1 minor or 3 minor criteria (borderline diagnosis); 1 major or 2 minor criteria from different categories (possible diagnosis).

Traditionally, three clinical phases of ARVC have been identified: the sub-clinical phase with concealed structural abnormalities (“concealed disease”), even thought SCD may be the first manifestation; the classical phase with palpitations, syncope and 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”) (43). However, while 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 gave a great impulse to the study of ARVC, due to its property to provide a non-invasive tissue characterization of the ventricular myocardium. While at the beginning the attention was focused on CMR ability to detect fatty tissue in the RV free wall, it became soon evident its limited diagnostic specificity in the absence of concomitant wall motion abnormalities, as well as the high degree of inter-observer variability (44). In the recent years, the advent of gadolinium enhancement technique to detect intramyocardial fibrosis gave a new impulse to the use of CE-CMR for ARVC diagnosis, since it represents a unique tool for identifying early/minor LV involvement, even in the absence of morpho-functional changes (23). 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, as to support the adoption of the broader term “arrhythmogenic cardiomyopathy”.

Electroanatomic mapping is an invasive tool able to identify the abnormal low voltage areas due to loss of electrically active myocardium (i.e. electroanatomic scar) through an endocardial catheter approach (45). 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 (46). However, due to the invasiveness, electroanatomic mapping is mainly
performed for differential diagnosis with idiopathic RV outflow tachycardia and to guide catheter ablation.

3. Risk stratification

The natural history of ARVC is characterized by a spectrum of ventricular arrhythmias ranging from PVCs to sustained VT or ventricular fibrillation (VF) (2-4). Typically, ventricular arrhythmias show a LBBB morphology pointing to an origin from the RV; the QRS axis usually suggests the site of origin, i.e. 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 due to VF varies among different series (25,40,47-56), 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 (40); to high mortality rate mostly due to SCD during a mean follow-up of 4.6 years (3.6% per year, in the series by Lemola et al. (54) (Table 2).

VF is the mechanism of SCD in young people with ARVC, which 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 (2,28,36). 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 pre-phenotypic phase of the disease (Fig. 1) (57,58).

The unpredictability of SCD in a subgroup of patients explain why there has been a trend toward ICD implantation once the disease was diagnosed, without an 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 remains still largely empiric.

Prior arrhythmic cardiac arrest and hemodynamically unstable VT have been demonstrated to be independent risk factors for life-saving ICD interventions (i.e. shock on VF episodes) in a large series of ARVC patients (59). On the other hand, patients implanted 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 reported by Canu et al. (50), a prior 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. (48). According to the data by Turrini et al. (60), 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 vs. only 2/12 patients who survived in the series by Blomstrom-Lundqvist et al. (47). Nava et al. (40) confirmed that syncope was the only clinical variable significantly associated with SCD in 19 ARVC probands, while 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 (61); in particular, the 9% annual incidence of shocks on VF among patients with prior syncope is comparable to that observed in patients with a history of cardiac arrest or sustained VT. Apparently contrast data come from a more recent study on prophylactic ICD for primary prevention carried out in the Johns Hopkins...
ARVC cohort (62), where a history of syncope was less often present than in the Darvin study (27% vs. 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%/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, at difference from other genetic cardiomyopathies and channelopathies in which syncope can be vaso-vagal or non-arrhythmic in origin, most syncopal episodes in ARVC are due to ventricular arrhythmias and are associated with a poor prognosis, similar to sustained VT or VF.

Among electrocardiographic parameters, right precordial QRS prolongation, QRS dispersion, and late potentials on signal-averaged ECG (SAECG), 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. (60), since 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 vs 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 (63). Moreover, a QRS dispersion >40ms was the strongest independent predictor of SCD in the ARVC series by Turrini et al. (60), with a sensitivity of 90% and a specificity of 77%. On the contrary, there are no data supporting a role of SAECG for arrhythmic risk
stratification in ARVC. In particular, late potentials were not predictive of ventricular arrhythmias in the series by Blomström-Lundqvist et al. (64) and Leclercq and Coumel (65), since 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. (66), 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. (53) on 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 (55) in 121 ARVC patients, in whom advanced RV dilatation/dysfunction and LV involvement were major clinical variables associated with an increase risk of SCD. Turrini et al. (66) 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 (67,68). 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 programmed ventricular stimulation (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 non-ischemic 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 (59,61). In the study of Wichter et al. (67), inducibility of VT or VF at pre-implant PVS of ARVC patients with previous history of cardiac arrest or sustained VT, demonstrated just a trend toward statistical significance for appropriate ICD interventions. In the recent Johns Hopkins series (61), inducibility at PVS was a significant predictor of any appropriate ICD therapy in primary prevention 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 (38,45), its value for risk stratification of SCD remains to be established. 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 due to VF, appropriate ICD intervention, and syncopal VT.

Published studies on ICD in ARVC, for either secondary or primary prevention of SCD, are providing useful insights for a therapy-based risk stratification. DARVIN I study (59) yielded the following predictors of appropriate ICD interventions: prior 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 syncope, LV involvement, early onset of symptoms and structural progression were the stronger predictors of SCD (52).
While there is general agreement that survivors of an episode of VF or sustained VT best benefit of ICD because of the high incidence of malignant arrhythmia recurrences (59) (Fig.2), the role of prophylactic ICD in ARVC patients with no previous history of sustained tachyarrhythmias or cardiac arrest is less clear (61). In the DARVIN II study, patients who received an ICD because of a prior syncope had a similar incidence of appropriate, life-saving interventions triggered by either VF or ventricular flutter (Vfl) as did patients with a history of aborted SCD/poorly tolerated sustained VT (Fig.3,4). On the other hand, asymptomatic patients had a favourable long-term outcome, regardless of familial SCD and electrophysiologic study findings. Finally, demonstration of non-sustained VT on 24-hour Holter monitoring and/or exercise testing in asymptomatic patients confers an increased risk of developing VT during the follow-up, although it did not significantly predict the occurrence of potentially lethal VF/Vfl (61).

More recently, the John Hopkins series identified clinical variables such as inducibility at PVS, the presence of non-sustained VT, proband status, and Holter monitoring PVCs >1,000/24 h as significant predictors of any appropriate ICD therapy, although their value for predicting life-saving ICD interventions on VF was not shown (62). Moreover, the presence of multiple risk factors incrementally increased the likelihood of appropriate ICD therapy with mutation status, electrocardiographic and major structural abnormalities not affecting this risk. Patients, especially family members with none of these markers, appear to be at low risk of life-threatening ventricular arrhythmias.

Sports activity has been shown to increase the risk of SCD by 5 fold in people affected by ARVC (69) (Fig. 5), since acute volume overload with RV stretching during effort and sympathetic stimulation are major triggers of life-threatening ventricular arrhythmias (70,71).
Additionally, mechanical stress may promote the underlying myocardial substrate accelerating disease progression. This explains why sport pre-participation screening with early detection of asymptomatic ARVC patients is lifesaving. The decline of SCD from 3.8/100,000 to 0.4/100,000 year after the implementation of the systematic screening in Northeast of Italy, was mostly due 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 (72). Accordingly, drugs such as beta-blockers or even ACE inhibitors might prevent the progression of disease; however, this is speculative and remains to be proven in asymptomatic or borderline AC patients and gene carriers.

For similar reasons, the cardiovascular system adaptation to increased plasma volume and cardiac output observed during pregnancy could also have an impact on ARVC progression (73). A careful clinical follow-up of women, particularly in the last trimester of pregnancy and puerperium, is recommended due to 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 (2,3,32,33). With the exception of the very malignant variant of ARVC due to TMEM43 gene mutation (74), genotype-phenotype correlations in desmosomal ARVC have failed to identify so-called “malignant mutations” as 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 non-carriers. 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.

4. **Current management.**

Besides lifestyle advice, therapeutic options in ARVC include antiarrhythmic drug therapy, catheter ablation and the ICD (2,3,75,76). Anti-arrhythmic drug therapy is used to reduce/prevent arrhythmias and, among patients with an ICD, to reduce both appropriate and inappropriate ICD interventions. Prospective and randomized studies on antiarrhythmic drugs in ARVC are not available and most of data are 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 (75,77). Sotalol at a dosage of 320-480 mg a day was the most effective drug, with an 68% overall acute efficacy rate. In a small subset of patients with non reentrant 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 was also effective, while class I antiarrhythmic drugs were only in a minority of patients (18%). Anyway, in long-term, sotalol or non pharmacologic treatments are preferentially used due to the high incidence of serious side effects of amiodarone.

Adequate monitoring of drug efficacy is fundamental in ARVC. In the experience of Wichter et al (75), 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 tested 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 put on antiarrhythmic drug at the discretion of the treating physician (78). Noteworthy, 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 taking 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 due to localized ARVC. The results of catheter ablation of ARVC-related VT varies 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 due to 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 (79); 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 (80), 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 (46,81), with no VT recurrence after 18+/-13 months
in 77% of treated patients in the Marchlinski series. However, higher number study populations are needed to confirm these preliminary data.

It is widely accepted that ICD therapy improves long-term prognosis and survival in ARVC patients at high risk of SCD (59,61,67,68,74,82-84) (Table 4). However, the significant rate of inappropriate interventions and complications, as well as the psychological repercussions mostly in the younger age group, strongly suggests the need to accurately stratify the individual arrhythmic risk before device implantation. The current threshold for ICD implantation differs in Europe (61) and in the US (62), being much higher in the former. Caution is particularly needed in patients who get misdiagnosed with ARVC mostly based upon CMR features and in fact do not have the disease (85).

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 (i.e. episodes of VF) derived from observational studies (3). The best candidates for ICD therapy are patients with prior cardiac arrest and those with VT with haemodynamically unstable VT (i.e. associated with syncope or shock); and patients with syncope which remains unexplained after exclusion of non-cardiac causes and vaso-vagal mechanisms. In this high risk group of patients, the rate of appropriate ICD intervention against life-threatening ventricular tachyarrhythmias is 8-10% per year and the estimated mortality reduction at 36 months of follow-up ranges from 24 to 35% (61).

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 (61).
This patient cohort carries a low arrhythmic risk over a long-term follow-up (ICD intervention rate <1 per year), in addition to a significant rate of device-related complications and inappropriate discharges.

Patients with well tolerated sustained VT or nonsustained on Holter or exercise testing have an intermediate arrhythmic risk (ICD intervention rate ~1-2% per year). In this patients subgroup, the decision for ICD implantation needs to be individualized; antiarrhythmic drug therapy (including beta-blockers) and/or catheter ablation seem to be a reasonable first-line therapy. Whether in the absence of syncope or significant ventricular arrhythmias, severe dilatation and/or dysfunction of RV, LV or both as well as early onset structurally severe disease require prophylactic ICD remains to be established: It is also a matter of debate whether the decision making to implant an ICD should take into account risk factors such as the presence of PVCs >1,000/24 h and/or non sustained VT, proband status, and inducibility at PVS, either alone or in combination, which though have been associated with an increased risk of any appropriate ICD interventions (mostly non life-threatening VT), have not been proved to significantly predict life-saving device shocks against VF (62).

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 al of 126 ARVC patients followed up for a mean period of 99±64 months, the annual incidence of thromboembolism was 0.5% (86). It is still debated whether prophylactic anticoagulation is needed in patients with RV aneurysms as well as with the left-dominant and biventricular subtypes of ARVC. Heart transplantation is the final therapeutic option in case of
refractory congestive heart failure and/or untreatable ventricular arrhythmias with incessant electric storms (87).

5. **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 “monogenetic” disease has evolved over the last decade into the current concept of the complex genetic disease characterized by marked intra- and inter-familial phenotype diversity. There is emerging evidence that a gene-dose effect (more than one “hit”) may be required for clinical disease expression. Modifiers genes and additional unknown disease causing genes are currently under investigation (88), facilitated by the advent of next generation sequencing techniques.

Besides 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 (88,89). Currently available and developing experimental ARVC animal models represent a potential valuable resource to answer to these questions (72,90-96). 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 (72). Furthermore, a load-reducing therapy (furosemide and nitrates) prevented training-induced development of ARVC in the same mouse model (94). If confirmed in large cohorts of patients, these data could support the use of drugs
such as beta-blockers and ACE inhibitors to prevent the disease progression in borderline or healthy gene mutation carriers.

Besides tissue biomarkers that arise early in the disease process, consisting in diminished immunoreactive signal for plakoglobin at intercalated disks (97), the role of blood biomarkers, such as circulating pro-inflammatory cytokines, markers of fibrosis and many others accompanying the onset and the clinical phases of disease progression need to be explored.

While LV involvement has been considered for a long-time 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. Diagnostic criteria are needed to properly and timely identify these patients, in order to better characterize this “new” cohort of ARVC patients, since current clinical data are almost exclusively derived from series of ARVC patients with the classic RV dominant disease variant (98,99). 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 due to desmosomal gene mutations might account for abnormal electrical coupling and/or ion channel dysfunction, leading to electrical instability even before ventricular structural remodeling. If proven, this revolutionary theory could dramatically change our approach in risk stratification and management of patients affected with ARVC.

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**Conflict of Interest Disclosures:** None
References:


voltage mapping and histologic evaluation of myocardial substrate in right ventricular outflow tract tachycardia. *J Am Coll Cardiol.* 2008;51:731-739.


2011;4:318-326.


### Table 1. Desmosomal genes in ARVC

<table>
<thead>
<tr>
<th>Author (ref)</th>
<th>Gene</th>
<th>Protein</th>
<th>Chromosome</th>
<th>OMIM*</th>
<th>Mode of inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>McKoy et al. (8)</td>
<td>JUP</td>
<td>Plakoglobin</td>
<td>17q21</td>
<td>#601214,</td>
<td>AR*</td>
</tr>
<tr>
<td>Asimaki et al. (17)</td>
<td></td>
<td></td>
<td></td>
<td>#611528</td>
<td>AD</td>
</tr>
<tr>
<td>Norgett et al. (11)</td>
<td>DSP</td>
<td>Desmoplakin</td>
<td>6p24</td>
<td>#605676</td>
<td>AR†</td>
</tr>
<tr>
<td>Rampazzo et al. (13)</td>
<td></td>
<td></td>
<td></td>
<td>#607450</td>
<td>AD</td>
</tr>
<tr>
<td>Gerull et al. (14)</td>
<td>PKP2</td>
<td>Plakophilin2</td>
<td>12p11</td>
<td>#609040</td>
<td>AD</td>
</tr>
<tr>
<td>Pilichou et al. (15)</td>
<td>DSG2</td>
<td>Desmoglein2</td>
<td>18q12</td>
<td>#610193</td>
<td>AD</td>
</tr>
<tr>
<td>Syrris et al. (16)</td>
<td>DSC2</td>
<td>Desmocollin2</td>
<td>18q12</td>
<td>#610476</td>
<td>AD</td>
</tr>
</tbody>
</table>

*AD: autosomal dominant; AR: Autosomal recessive
*Naxos disease; † Carvajal syndrome
Table 2. Annual mortality rate, heart failure and sudden cardiac death in ARVC series

<table>
<thead>
<tr>
<th>Author (ref)</th>
<th>Year</th>
<th>N pts</th>
<th>FU (yrs)</th>
<th>ARVC related death, n (annual mortality rate, %)</th>
<th>HF death</th>
<th>SC death</th>
<th>HTx (%)</th>
<th>ICD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blomstrom et al (47)</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 (48)</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 &amp; Coumel (49)</td>
<td>1989</td>
<td>58</td>
<td>8.8</td>
<td>4 (0.8)</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Canu et al (50)</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 (51)</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 (40)</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 (52)</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 (53)</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 (35)</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 (54)</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 (55)</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 (25)</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 (56)</td>
<td>2011</td>
<td>96</td>
<td>128</td>
<td>12 (0.09)</td>
<td>6</td>
<td>6</td>
<td>7 (7.3)</td>
<td>12 (12.5)</td>
</tr>
</tbody>
</table>

FU= follow-up; HF= heart failure; SC=sudden cardiac; HTx= heart transplantation; NR=not reported

*homozygous carriers; #median
**Table 3. Risk factors for sudden death in ARVC**

<table>
<thead>
<tr>
<th>Strongest risk factors</th>
</tr>
</thead>
<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>Physical exercise/sport activity</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other recognized risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young age at diagnosis</td>
</tr>
<tr>
<td>Hemodynamically stable sustained VT</td>
</tr>
<tr>
<td>Non sustained VT</td>
</tr>
<tr>
<td>Severe RV dysfunction</td>
</tr>
<tr>
<td>LV involvement</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Questionable risk factors</th>
</tr>
</thead>
<tbody>
<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 CARTO-system)</td>
</tr>
<tr>
<td>Molecular genetics</td>
</tr>
<tr>
<td>Proband status</td>
</tr>
<tr>
<td>PVC count Holter &gt;1000/24 h</td>
</tr>
</tbody>
</table>

VT: ventricular tachycardia; SCD: sudden cardiac death; RV: right ventricular; LV: left ventricular; PVC
Table 4. Major series of implantable cardioverter defibrillator in ARVC

<table>
<thead>
<tr>
<th>Author (ref)</th>
<th>Year</th>
<th>Pts (n)</th>
<th>Study Design</th>
<th>Men (%)</th>
<th>FU (mo)</th>
<th>Primary prevention (%)</th>
<th>Mortality overall (%)</th>
<th>Appropriate ICD (%)</th>
<th>Life-saving ICD (%)</th>
<th>Complications (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breithardt (83)</td>
<td>1994</td>
<td>18 SC</td>
<td>72</td>
<td>17±11</td>
<td>0</td>
<td>0</td>
<td>59</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Link (84)</td>
<td>1997</td>
<td>12 SC</td>
<td>58</td>
<td>22±13</td>
<td>0</td>
<td>8</td>
<td>67</td>
<td>50</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Tavernier (82)</td>
<td>2001</td>
<td>9 SC</td>
<td>89</td>
<td>32±24</td>
<td>0</td>
<td>0</td>
<td>78</td>
<td>44</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Corrado (59)</td>
<td>2003</td>
<td>132 MC</td>
<td>70</td>
<td>39±25</td>
<td>22</td>
<td>3</td>
<td>48</td>
<td>24</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Wichter (67)</td>
<td>2004</td>
<td>60 SC</td>
<td>82</td>
<td>80±43</td>
<td>7</td>
<td>13</td>
<td>68</td>
<td>40</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Rougin (68)</td>
<td>2004</td>
<td>42 MC</td>
<td>52</td>
<td>42±26</td>
<td>40</td>
<td>2</td>
<td>78</td>
<td>NR</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Hodgkinson (74)</td>
<td>2005</td>
<td>48 MC</td>
<td>63</td>
<td>31</td>
<td>73</td>
<td>0</td>
<td>70</td>
<td>30</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Corrado (61)</td>
<td>2010</td>
<td>106 MC</td>
<td>70</td>
<td>39±25</td>
<td>100</td>
<td>0</td>
<td>24</td>
<td>17</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Bhonsale (62)</td>
<td>2011</td>
<td>84 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>
<td></td>
</tr>
</tbody>
</table>

FU= follow-up; SC= single center; MC=multicenter; NR=not reported
Figure Legends:

**Figure 1.** Substrates and pathophysiologic mechanisms of ventricular arrhythmias in the different phases of ARVC.

**Figure 2.** DARVIN I Study: A) Kaplan-Meier analysis of actual patient survival (upper line) compared with survival free of VF/VfI (inner line) 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. B) Kaplan-Meier curves of freedom from ICD interventions on VF/VfI for different patient subgroups stratified for clinical presentation. Patients who received an ICD because of sustained VT without hemodynamic compromise had a significantly lower incidence of VF/VfI during the follow-up (from Corrado et al, 59).

**Figure 3.** DARVIN II Study: (A) Kaplan-Meier analysis of cumulative survival from any appropriate ICD interventions. (B) Kaplan-Meier analysis of survival free of VF/VfI compared with actual patient survival. The estimated mortality reduction at 48 months of follow-up is 23% (i.e. the difference between the actual patient survival rate of 100% and VF/VfI-free survival rate of 77%) (from Corrado et al, 61).

**Figure 4.** DARVIN II Study: Kaplan-Meier analysis of freedom from any appropriate ICD interventions (A) and shock therapies on VF/VfI (B), stratified by syncope (from Corrado et al, 61)

**Figure 5.** Incidence and relative risk (RR) of SCD from major cardiovascular causes among young athletes and non-athletes. ARVC = arrhythmogenic RV cardiomyopathy; CAD=coronary artery disease; CCA=congenital coronary artery anomalies (modified from Corrado et al, 69)

**Figure 6.** Pyramid of risk stratification for ICD implantation in ARVC (modified from Corrado et al, 3)
Arrhythmic risk

**Highest** 8-10% / year

- Aborted SD
- Hemodynamically unstable sustained VT
- Syncope

**Intermediate** 1-2% / year

- Hemodynamically stable sustained VT
- Non-sustained VT (during Holter/exercise test)

- Severe dilatation and/or dysfunction of RV, LV or both
- Early onset structurally severe disease (age < 35 years)

**Lowest** <1% / year

- Proband or relatives fulfilling Task Force criteria for ARVC, regardless of family history of SD or inducibility at PVS (in the absence of syncope, VT, or severe ventricular dysfunction)

ICD implantation

- Mandatory
- Individualized
- Unjustified
Arrhythmogenic Right Ventricular Cardiomyopathy
Cristina Basso, Domenico Corrado, Barbara Bauce and Gaetano Thiene

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