Arrhythmogenic cardiomyopathies (AC): diagnosis, risk stratification and management

A. Protonotarios[1,2], P. M. Elliott[1,2]

[1] UCL Institute of Cardiovascular Science, University College London, Gower Street, London, UK

[2] Inherited Cardiovascular Disease Unit, Barts Heart Centre, London, UK

Corresponding Author:

P. M. Elliott, MBBS; MD; FRCP; FESC; FACC

UCL Institute for Cardiovascular Science

Paul O'Gorman Building room G26

University College London

72 Huntley Street

London, WC1E 6DD

Email: perry.elliott@ucl.ac.uk

Word count: 3800

Learning Objectives

- To recognise AC as a rare but important cause of sudden cardiac death and heart failure.
- To raise awareness of the broader phenotype of classical arrhythmogenic right ventricular cardiomyopathy that includes left ventricular predominance and arrhythmogenic dilated cardiomyopathy phenotypes.
- To understand the clinical features of AC and the clinical approach to diagnosis.
- To be able to assess the arrhythmic risk of patients and relatives with AC.

Introduction

Phenotype is defined as a set of observable characteristics of an individual resulting from the interaction of their genotype with the environment. It differs from "disease" in that it does not reflect the mechanism by which it is produced. In 1982, the term arrhythmogenic right ventricular dysplasia (ARVD) was first used to describe a clinical phenotype characterised by ventricular arrhythmias of left bundle branch block configuration accompanied by right ventricular dilatation, wall motion abnormalities and fibrofatty replacement of the myocardium [1]. Arrhythmogenic right ventricular *cardiomyopathy* (ARVC) became the preferred descriptor when subsequent histopathological analysis revealed that myocyte atrophy as a consequence of progressive cell death occurred after birth [2] [3]. Initial clinical diagnostic criteria for ARVC were based upon descriptions of patients with advanced disease [4], but discovery of its genetic basis, and the phenotyping of large patient cohorts including relatives, revealed a broader disease spectrum in which right and left ventricles can be involved [5]. The disease paradigm has expanded further with the recognition of new disease genes causing similar phenotypes. Hence, terms such as *left dominant arrhythmogenic cardiomyopathy*, *arrhythmic dilated cardiomyopathy* or simply *arrhythmogenic cardiomyopathy* (AC) are increasingly used to describe the clinical phenotype observed in a family of disorders in which frequent ventricular arrhythmia and dysfunction of one or both ventricles are the defining features. In this article, we review this emerging concept with a focus on the genetics, and clinical presentation of different forms of AC and a diagnostic approach based on recognition of particular clinical traits (Figure 1).

PHENOTYPES ENCOMPASSED BY THE TERM ARRHYTHMOGENIC CARDIOMYOPATHY

(1) Arrhythmogenic right ventricular cardiomyopathy (ARVC)

Since the 1980s, ARVC has been defined as a progressive primary heart muscle disorder characterised by replacement of cardiomyocytes with fat and fibrosis underlying structural and functional abnormalities of the right ventricle (RV). The diagnosis of ARVC is based on consensus recommendations, originally proposed in 1994 and later revised in 2010 [4] [6]. They are relatively complex, compared to other cardiomyopathies (e.g. hypertrophic cardiomyopathy), and rely on integration of right ventricular morphology and function (assessed by echocardiography, angiography and/or cardiac magnetic resonance imaging),

histopathological analysis of endomyocardial biopsy, electrocardiography (ECG), arrhythmia, family history and molecular genetic analysis (Table). Quantitative parameters based on comparison with normal data are included in the criteria.

(2) Left Dominant Arrhythmogenic Cardiomyopathy

By definition ARVC is a right ventricular disease, but detailed phenotypic characterization of patients and family members has revealed that the left ventricle (LV) is frequently involved. Three main patterns of cardiac involvement are observed: 1) predominant right ventricular disease, with minor or absent left ventricular involvement; 2) biventricular disease, when both ventricles are affected; and 3) left dominant disease that is characterized by mild or absent right ventricular involvement[5][7]. The terminology used to describe this spectrum is poorly defined and at times confusing as it overlaps with current concepts of dilated cardiomyopathy[8].

(3) Arrhythmogenic Dilated Cardiomyopathy (ADC)

In a recent registry study, arrhythmogenic dilated cardiomyopathy (DCM) was defined as a DCM phenotype with 1 or more of the following: (1) unexplained syncope (likely due to ventricular tachyarrhythmia); (2) rapid non-sustained ventricular tachycardia defined as ≥5 consecutive ventricular beats lasting <30 seconds, with a rate ≥150/min on 24-hour Holter monitoring; or ≥1000 premature ventricular contractions in, or ≥50 couplets, in 24 hours[9]. By these criteria, one-third of DCM patients had an arrhythmogenic phenotype that was associated with an increased risk of arrhythmia during follow-up. A family history of ventricular arrhythmias predicted a poor prognosis and an increased risk of sudden cardiac death (SCD).

GENETICS AND PHENOTYPE CORRELATION

Key to discovery of the genetic basis of ARVC was its association with palmoplantar keratoderma and woolly hair in Naxos Disease, which is inherited as an autosomal recessive trait with full penetrance by adolescence[10]. A homozygous two-nucleotide deletion in the gene encoding plakoglobin (JUP) was identified[11]. Furthermore, a homozygous recessive mutation in the gene encoding desmoplakin (DSP) was identified in people with a similar cardiocutaneous phenotype (Carvajal syndrome) associated with highly arrhythmic DCM[12].

Following identification of desmosomal mutations in recessive disease, other mutations in genes encoding the five desmosomal proteins including plakophilin-2 (PKP2), desmoglein-2 (DSG2) and desmocollin-2 (DSC2), DSP and JUP were identified in cases of autosomal dominant disease[13-19]. PKP-2 mutations represent around 35%–40% of total ARVC cases[20], followed by mutations in DSP, DSG2 and DSC2 (about 15-20%)[21]. Mutations in JUP are very rare and account for less than 5% and are often absent in many ARVC cohorts[22].

Desmosomal protein gene mutations became a defining feature of ARVC and were included in consensus task force criteria for its diagnosis[6]. However, this purist concept has become difficult to sustain with the identification of mutations in non-desmosomal genes in patients fulfilling current diagnostic criteria for ARVC [23]. A number of non-genetic disorders also mimic the disease, notably myocarditis. Several genes encoding non-desmosomal proteins including desmin (DES), transmembrane protein 43 (TMEM43), transforming growth factor β-3 (TGFB3), lamin A/C (LMNA), titin (TTN), phospholamban (PLN), and filamin C (FLNC) have been implicated in phenotypes within the spectrum of arrhythmogenic cardiomyopathy.

DES mutations lead to heterogeneous myopathies ranging from skeletal muscle disease to isolated cardiomyopathy[24]. So far, less than 10 pathogenic variants linked to AC have been identified in DES gene.

A mutation in the gene encoding *TMEM43* was identified in a founder population in Newfoundland, Canada[25]. Five mutations have been described so far resulting in a clinical phenotype that presents significantly earlier in males, shows biventricular involvement and is characterized by a high incidence of premature SCD and severe heart failure in survivors[26].

Genetic alterations in LMNA are associated with a heterogeneous group of disorders commonly named 'laminopathies,' including dilated cardiomyopathy associated with a high incidence of conduction disease and ventricular arrhythmia. Male sex is associated with higher incidence of malignant ventricular arrhythmias and heart failure. In 2012, a genetic study in a cohort of 108 ARVC patients identified mutations in the LMNA gene in 4% of affected individuals[27]. The clinical phenotype was associated with mild systolic LV dysfunction, atrial arrhythmias and conduction system disease.

Mutations in TTN and PLN are commonly associated with DCM. Eight missense mutations in the TTN gene have been reported in ARVC patients [28] and a founder PLN

mutation has been linked to Dutch families with both DCM and ARVC phenotypes [29].

Mutations in the FLNC gene have been associated with myofibrillar myopathies. Genetic screening of patients with inherited cardiomyopathies and sudden death has been identified FLNC mutations in patients with an overlapping phenotype of dilated and left-dominant arrhythmogenic cardiomyopathies. The phenotype is characterised by variable degrees of LV dilation and systolic dysfunction, prominent subepicardial and/or intramyocardial fibrosis of the LV, frequent ventricular arrhythmias, and sudden cardiac death[30].

Recent studies have suggested that mutations in SCN5A may account for a small portion of the ARVC phenotype cohorts[31]. This is consistent with multiple studies which have demonstrated that desmosomal proteins are associated with altered kinetics of the sodium current in cardiomyocytes[32], a manifestation which precedes structural abnormalities, as seen in a DSG2 mouse model[33]. Finally, mutations in the genes encoding for cadherin 2 and αT-catenin have been very rarely identified among patients with AC[34 35].

A CLINICAL APPROACH TO THE DIAGNOSIS OF AC

Distinction between the various AC phenotypes is more than a simple matter of nosology as emerging evidence suggests that aetiology impacts substantially on the natural history and, by implication, treatment of individual patients. Current consensus recommendations (2010 Task Force Criteria) for diagnosis of ARVC focus predominantly on classical signs of right ventricular disease coupled with histology and genotype, whereas DCM is a much simpler concept defined only by left ventricular size and function with no reference to ECG, genetics or cardiac histology. A recent European Society of Cardiology position statement has recognised that there are scenarios such as preclinical or early disease in relatives of people with genetic forms of DCM and ARVC that do not fulfil conventional diagnostic criteria or fall into an overlap where they can be classified into different disease groups[8]. A new category of *hypokinetic non-dilated cardiomyopathy* has been proposed to account for some of these, but this also fails to capture the not infrequent scenario of isolated LV scarring in the absence of wall motion abnormality (Figure 2).

While consensus still needs to be reached on an integrated classification of AC, there are some common principles that can orient clinical diagnostic and management pathways. AC should be considered in the presence of the following:

a. *Structural abnormalities of the myocardium including regional or global systolic dysfunction or myocardial scar in <u>either</u> ventricle, unexplained by ischaemic heart disease or an acute inflammatory trigger by an identifiable cause such as viral infection or exposure to a toxic agent.*

b. *Frequent ventricular ectopy, sustained or non-sustained ventricular tachycardia, or unexplained cardiac arrest.*

There are a number of features that can suggest specific aetiologies in people with systolic dysfunction on either or both ventricles associated with frequent ventricular arrhythmia.

(i) Family History

Genetic disease is reported in up to 60% of reported AC cases. Detailed family history and familial evaluation are important aids to diagnosis and identify asymptomatic individuals at risk of disease complications. A family history of AC, ventricular arrhythmia, and young sudden deaths are important pointers to a diagnosis. The presence of atrioventricular block or atrial fibrillation in family members can indicate a specific genetic defect (e.g. LMNA, SCN5A) particularly if co-existing with young sudden cardiac deaths. Implantable cardioverter defibrillator (ICD) implants or heart failure in relatives should also be noted. A clinical episode of acute myocarditis might be significant in an individual suspected of having AC as emergence of cardiac symptoms with such episodes has been reported in JUP homozygotes with Naxos syndrome and in dominant AC families [36-38]. This is further supported by experimental evidence in a DSG2 mouse model where marked inflammation preceded the development of the overt fibrosis[39].

(ii) Physical Examination

Cardiovascular examination is important in the assessment of all patients, but the frequently subtle pathology of AC means that it may be non-contributory except in advanced disease with ventricular dilatation and systolic impairment [10 40 41] On the other hand, examination of the skin and hair in the affected patients and their family members can be helpful. Woolly

hair and palmo-plantar hyperkeratosis is typical of JUP homozygotes and is also observed in heterozygous carriers of mutations in DSP[42]. Additionally, homozygous DSC2 traits associate with late onset AC with palmoplantar keratosis[43].

Several skeletal myopathies are associated with an arrhythmogenic cardiomyopathy phenotype. These include proximal muscle weakness that resembles limb-girdle muscular dystrophy caused by FLNC mutations[44]. Desmin mutations are also associated with a variety of myopathies, the most common being a distal leg muscle weakness spreading to proximal muscles and weakness in the trunk, neck, and facial muscles in some patients [45].

(iii)   Electrocardiography

Ventricular Arrhythmias

Ventricular arrhythmias are a defining feature of AC and take the form of ventricular extrasystoles (VES), non-sustained or sustained ventricular tachycardia (VT) and ventricular fibrillation (VF). They most commonly arise from the right ventricle in typical ARVC (Figure 3) but left ventricular arrhythmias are seen in the biventricular and left-dominant sub-phenotypes [46].

Current taskforce criteria for ARVC suggest that more than 500 VEs in 24h is a minor criterion for the disease [6]. However, daily variability in the number of VEs is common and may result in underdiagnosis[47]. An association between the total number of VEs per 24h and the arrhythmic potential for unstable ventricular arrhythmias has been demonstrated[48]. VEs may also present prior to the formation of structural/functional alterations identifiable with conventional imaging[49]; in ARVC this phenomenon has been attributed to early loss of junctional connexin 43 and micro-re-entry [49].

Depending on the underlying ventricular origin, sustained monomorphic VT may have left bundle branch block (LBBB) and superior axis or right bundle branch block (RBBB) morphology [50] [51]. Other morphologies such as LBBB with inferior axis mimicking idiopathic right ventricular outflow tract (RVOT) tachycardia also occur[52]. VF is the predominant mechanism underlying sudden cardiac death in AC and is related to active disease progression[53]. Paradoxically, ventricular arrhythmias are often less frequent in patients with long standing AC and extensive myocardial scarring [54].

Repolarization abnormalities

Precordial T wave inversion (TWI), up to V3, is observed in 4% of healthy women and 1% of men but its presence in the anterior precordial leads in the absence of RBBB raises the possibility of classical ARVC where they are present in more than 70% of patients [6]. Electrophysiological studies show a correlation between the electroanatomic voltage scar area in the right ventricle with the extent of TWI in the anterior leads[55]. In other forms of AC, T wave abnormalities can extend to all precordial leads or be confined to the inferolateral leads (suggestive of the left dominant form) [56]. TWI can precede structural abnormalities seen on conventional imaging. [48 55 57].

Depolarization abnormalities

Myocardial degeneration and fibrosis in AC leads to the formation of slow conducting myocardial regions and abnormalities in depolarization on the surface ECG. The type and frequency of depolarization abnormalities is dependent on the sub-phenotype of AC. Typical ARVC, where right ventricular disease predominates, is characterized by prolonged terminal activation duration (≥55 ms) of the QRS complex in leads V1-V3 and in more severely affected cases epsilon waves may form [58] (See Figure 3). Epsilon waves defined as reproducible low-amplitude signals after the end of the QRS complex up to the onset of the T wave are detected in approximately 20-30% of ARVC cases. They are usually present in the anterior precordial leads and can extend to infero-lateral leads[59]. It is important that they are strictly defined as waves separated from QRS complex by an isoelectric line to avoid misinterpretation of fragmentation in the final portion of the QRS complex [60]. Epsilon waves have been associated with significant structural abnormalities of the right ventricle, particularly of the right ventricular outflow tract[59]. Signal averaged ECG is another means of detecting delayed late potentials and it can be positive in all forms of AC as it represent fibrosis in either ventricles [61].

Abnormal depolarization is also demonstrated by three-dimensional electroanatomic voltage mapping which can demonstrate low-voltage areas caused by fibrofatty replacement of the myocardium[62]. This technique can be useful in differentiating AC from

RVOT tachycardia and may aid in the risk stratification for life threatening arrhythmias[63]. An epicardial mapping approach is sometimes helpful as disease is mostly subepicardial[64].

A relatively new concept in the AC phenotype is the presence of delay in the specialised conduction system. In typical ARVC the most common conduction abnormality seen is RBBB which usually signifies advanced disease, masking altogether epsilon waves, TAD and late potentials on signal-averaged ECG[59]. A recent study has suggested that first degree atrioventricular (AV) block is present in 1 in 4 AC patients and it is an independent risk factor for heart failure hospitalizations[65]. However, within the broad spectrum of AC, AV conduction defects are seen especially in patients with DES, LMNA, Titin or FLNC mutations. These may range from first to third degree AV block [30 66-68].

Imaging

Classification of the structural abnormalities that can occur in different forms of AC is a considerable challenge because they are so diverse and may not align with existing disease paradigms. Nevertheless, a relatively simple approach to the multimodality assessment of cardiac form and function is invaluable in orienting diagnosis and treatment decisions.

The essential components of the imaging assessment of AC include the following:

1   Assessment of global and regional function of the left and right ventricle.

2   Assessment of the presence and distribution of fibrosis and adipose tissue in both ventricles.

3   Exclusion of co-existing cardiac or extra-cardiac pathologies that can result in phenocopies.

In classical ARVC caused by desmosomal mutations, wall motion abnormalities (dyskinesia, akinesia or aneurysm formation) are most common in the anterior, lateral, apical and postero-diaphragmatic wall of the RV (Figure 4). In advanced disease, the RV apex and infero-lateral LV wall may be involved. In left dominant forms of AC, there may only be scarring in the posterolateral LV segments, often without wall motion abnormalities (Figure 2). In both ARVC and left dominant AC, severe dilatation of either ventricle is rare until the very late stages of disease. Circumferential scarring is described in mutations causing the left dominant forms of the disease such as FLNC and DSP mutations[30 69] in contrast to

cardiac sarcoidosis where scarring is often in the basal segments of the LV and septum which are usually spared in genetic forms of AC [70]. Chest imaging showing lymphadenopathy or pulmonary infiltrates should prompt consideration of sarcoidosis in the differential diagnosis.

Other important phenocopies not to miss include intra- or extra-cardiac shunts (suggested by evidence for right ventricular pressure or volume overload, pulmonary hypertension and tricuspid regurgitation) and cardiac displacement associated with thoracic cage abnormalities (pectus deformity, kyphoscoliosis) or partial absence of the pericardium.

MANAGEMENT

Management of AC can be subcategorized into symptom relief and the prevention of sudden cardiac death.

Lifestyle modification

All patients with AC should be advised to avoid participation in sports at a professional level and to pursue recreational exercise cautiously as it has been demonstrated that there is a link between exercise intensity and disease development and arrhythmic risk in a number of sub-phenotypes [71-73]. Reduction in exercise duration and dose has been correlated with decrease in ventricular arrhythmias, but not enough to warrant modification of ICD-indications[74].

Pharmacological management

Pharmacological management is used to control symptoms caused by ventricular arrhythmias or heart failure. However, anti-arrhythmic drugs do not reduce the probability of sudden cardiac death and few data exist about their efficacy in different forms of AC. In ARVC, amiodarone alone or in combination with beta blockers appears to be the most effective strategy but sotalol is frequently used as a long-term option in young individuals[75]. Evidence about prophylactic use of b-blockers or amiodarone in asymptomatic individuals do not exist and so they are not commonly used.

The management of right and left heart failure symptoms is based on conventional heat failure management strategies but there are no data on the efficacy of angiotensin-converting-enzyme inhibitors, β-blockers or mineralocorticoid-receptor-antagonists in AC [76].

Thrombo-embolic risk in patients with AC is uncertain as there is only a single study that identifies reporting an annual incidence of 0.5%[77]. Certain subgroups of patients, such as those with LMNA mutations have been demonstrated to have higher thrombo-embolic risk[78]. It is suggested that patients with AC are anticoagulated in the presence of documented intra-cavitary thrombus or systemic thromboembolism[79]. The lack of evidence for risk stratification of patients with atrial fibrillation leads to the decision for anticoagulation being made on individual basis but use of the CHA_2DS_2VASc score is untested in this population.

Ablation of arrhythmias

VT often arises as the consequence of macro-reentry around scars[80]. Catheter ablation can be used to reduce the risk of developing sustained ventricular arrhythmia with reported success in up to 60-80%, especially with an epicardial approach[81]. However, due to the progressive nature of the disease, recurrence is frequent and catheter ablation should always be combined with optimal pharmacological therapy.

Heart Transplantation

Heart transplantation is reserved for those patients with refractory ventricular arrhythmias and in patients with intractable heart failure where conventional management is not able to provide an acceptable quality of life[79].

Risk stratification and indications for ICD implantation

One of the primary goals in the management of AC is to identify patients at high risk of SCD who may benefit from prophylactic ICD implantation. Neither pharmacologic treatment or catheter ablation has been shown to reduce sudden cardiac death risk. The majority of data on risk stratification of AC are based on studies of the ARVC phenotype[79]. Arrhythmic risk in this context has been stratified in three categories: high, intermediate and low (Figure 5). The intermediate risk group is further subcategorised according to the presence of major and minor risk factors. Major risk factors include syncopal episodes unrelated to

extracardiac causes or reflex mediated changes in vascular tone and/or heart rate, non-sustained ventricular tachycardia and moderate left or right ventricular dysfunction. Minor risk factors include many features for which prognosis evidence is weak or absent. These include proband status, male gender, compound or digenic heterozygosity, extent of TWI in the inferior leads or beyond lead V3 from the precordial leads, QRS fragmentation, extent of electroanatomic voltage mapping scar, inducible VT/VF and young age[48 50 57 63 82-88]. ICDs are generally indicated for high risk patients and are considered for those with major risk factors that belong to the intermediate risk group. Implantation of an ICD in patients that have only minor risk factors may be considered but only after a careful discussion of the risks and benefits. Finally, ICD implantation is contraindicated in patients without risk factors or in healthy mutation carriers[79].

Left dominant forms of AC are under-represented in most of risk stratification studies and data regarding stratification of arrhythmic risk in these patients do not exist. Similarly, while patients with the arrhythmogenic forms of dilated cardiomyopathy are known to have higher arrhythmic risk than the other DCM patients, there are no clinical tools available to quantify this risk and to guide ICD implantation[9]. Nevertheless, emerging data suggest that ICD implantation is reasonable in subtypes of AC associated with mild-moderate left ventricular dysfunction such as disease caused by Filamin C, LMNA and DES mutations. In LMNA and DES related disease there is often a pacing indication as well as a high risk of ventricular arrhythmia.

Follow up

Study of patients in AC cohorts with long follow up has revealed that disease progression is common[89]. Periodic reassessment of the arrhythmic risk is important as evolution of the ECG abnormalities occurs more frequently than structural abnormalities[90]. In general, healthy mutation carriers should also be evaluated, once every one to two years, with 24h tape, ECG and standard echocardiogram and whenever new symptoms such as syncope or palpitations appear.

Family screening

Screening of the first-degree family members is advisable as it identifies other individuals with the disease who are potentially at risk for sudden cardiac death. The presence of a

pathogenic mutation in the proband permits cascade genetic testing of relatives and the exclusion of mutation-negative family members from further follow-up. However, physicians should be cautious with interpretation of genetic results within this context and only discharge patients when it is certain that a genetic variant is pathogenic and there is no possibility of additional pathogenic genetic variants in the family. As the disease usually develops from adolescence onwards, clinical screening at yearly to two-yearly intervals should be considered from the age of 10-12 years[91].

Summary and conclusions

AC represents a diverse group of myocardial disorders that can have a more malignant arrhythmic course compared to other cardiomyopathies. They are primarily defined by the high burden of ventricular arrhythmia and structural abnormalities of varying severity. Diagnosis, risk stratification and management relate to aetiology.

Key points

- AC refers to a group of myocardial disorders that have a high burden of ventricular arrhythmias and can affect one or both ventricles.
- In contrast to classical DCM, patients with AC can have a malignant arrhythmic course even with mild ventricular dysfunction.
- Three major sub-phenotypes are classical ARVC, left dominant arrhythmogenic cardiomyopathy and arrhythmogenic DCM.
- AC is familial in about 60% of cases.
- Diagnostic criteria and management guidance exist for ARVC but further studies are required to define other forms of AC
- ECG abnormalities can precede overt structural manifestations.
- Symptomatic presentation of ventricular arrhythmias or a history of arrhythmic cardiac arrest in an otherwise normal myocardium should raise suspicion of an early AC phenotype.
- Exercise may promote disease progression and ventricular arrhythmia.
- Follow up is important as phenotype progression is common.

Table 1: Revised task force criteria for the diagnosis of ARVC

<table>
<tr><td colspan="3" align="center">Revised Task Force Criteria for the diagnosis of ARVC</td></tr>
<tr><td>Features</td><td>Major</td><td>Minor</td></tr>
<tr>
<td>Arrhythmias</td>
<td>•Non-sustained or sustained ventricular tachycardia of left bundle-branch block morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL).</td>
<td>•Non-sustained or sustained ventricular tachycardia of RV outflow configuration, LBBB-morphology with inferior axis (positive QRS in leads II, III, and aVF and negative in lead aVL) or of unknown axis).

•> 500 VES /24 hours (Holter)</td>
</tr>
<tr>
<td>Repolarization abnormalities</td>
<td>•Inverted T waves in right precordial leads (V1, V2, and V3) or beyond in individuals >14 years of age (in the absence of complete RBBB).</td>
<td>•Inverted T waves in leads V1 and V2 in individuals > 14 years of age (in the absence of complete RBBB) or in V4, V5, orV6

•Inverted T waves in leads V1, V2, V3 and V4 in individuals > 14 years of age in the presence of complete RBBB</td>
</tr>
<tr>
<td>Depolarization abnormalities</td>
<td>•Epsilon waves (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V1 to V3).</td>
<td>•Late potentials by SAECG in ≥1 of 3 parameters in the absence of a QRS duration of 110 ms on the standard 12-lead ECG:

- Filtered QRS duration ≥ 114 ms.
- Duration of terminal QRS less than 40 mV (low-amplitude signal duration) ≥ 38 ms.
- Root-mean-square voltage of terminal 40 ms ≤ 20 mV.

•Terminal activation duration of QRS ≥ 55 ms (measured from the nadir of the S wave to the end of the QRS, including R', in V1, V2, or V3) in the absence of complete RBBB.</td>
</tr>
<tr>
<td>Structural wall</td>
<td>•Regional RV akinesia, dyskinesia, or aneurysm and 1 of</td>
<td>•Regional RV akinesia or dyskinesia and 1 of the following</td>
</tr>
</table>

motion abnormalities, by 2D echo	the following (end diastole): - PLAX RVOT ≥ 32 mm (corrected for body size [PLAX/BSA] ≥19 mm/m^2) - PSAX RVOT ≥ 36 mm (corrected for body size [PSAX/BSA] ≥21 mm/m^2) - or fractional area change ≤33%	(end diastole): - PLAX RVOT ≥ 29 to <32 mm (corrected for body size [PLAX/BSA] ≥16 <19 mm/m^2) - PSAX RVOT ≥ 32 to <36 mm (corrected for body size [PSAX/BSA] ≥18 to <21 mm/m^2) - or fractional area change >33% to ≤ 40%
by CMR	•Regional RV akinesia or dyskinesia or dyssynchronous RV contraction **and** 1 of the following: - Ratio of RV end-diastolic volume to BSA ≥ 110 mL/ m^2 (male) or ≥ 100 mL/ m^2 (female) - or RV ejection fraction ≤ 40%	•Regional RV akinesia or dyskinesia or dyssynchronous RV contraction **and** 1 of the following: - Ratio of RV end-diastolic volume to BSA ≥ 100 mL/m^2 to <110 mL/m^2 (male) or ≥ 90 mL/ m^2 to <100 mL/m^2 (female) - or RV ejection fraction >40% to ≤45%
by RV angiography	•Regional RV akinesia, dyskinesia or aneurysm	
Tissue characterization of wall	•Residual myocytes <60% by morphometric analysis (or <50% if estimated), with fibrous replacement of the RV free wall myocardium in ≥ 1 samples, with or without fatty replacement of tissue on endomyocardial biopsy.	•Residual myocytes 60% to 75% by morphometric analysis (or 50% to 65% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 samples, with or without fatty replacement of tissue on endomyocardial biopsy.
Family history	•ARVC/D confirmed in a first-degree relative who meets current Task Force criteria. •ARVC/D confirmed pathologically at autopsy or surgery in a first degree relative. •Identification of a pathogenic* mutation categorized as associated or probably associated with ARVC/D in	•History of ARVC/D in a first-degree relative in whom it is not possible or practical to determine whether he meets current Task Force criteria. •Premature sudden death (<35 years of age) due to suspected ARVC/D in a first-degree relative. •ARVC/D confirmed pathologically or by current Task Force

	the patient under evaluation.	Criteria in a second degree relative.

BSA, body surface area; LBBB, left bundle branch block; PLAX, parasternal long axis; PSAX, parasternal short axis; RBBB, right bundle branch block; RV, right ventricular; RVOT, right ventricular outflow tract; SAECG, signal averaged ECG.

* A pathogenic mutation is a DNA alteration associated with ARVC that alters or is expected to alter the encoded protein, is unobserved or rare in a large, non-ARVC, control population, and either alters or is predicted to alter the structure or function of the protein or has demonstrated linkage to the disease phenotype in a conclusive pedigree.
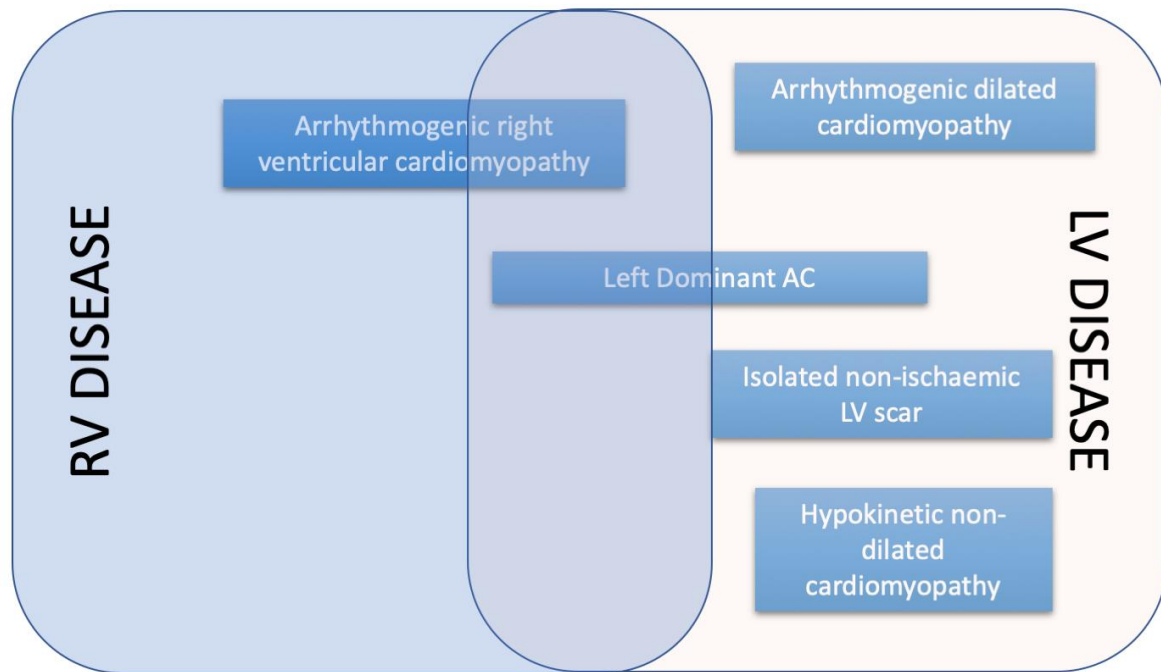
Figure 1: Schematic representation of the distribution of disease between the two ventricles of the currently used nosologic definitions. Arrhythmogenic right ventricular cardiomyopathy, most commonly affects the right ventricle or it is biventricular. In left-dominant arrhythmogenic cardiomyopathy the left ventricle is predominantly affected but there are cases with minor right ventricular involvement. Hypokinetic non-dilated cardiomyopathy, arrhythmogenic dilated cardiomyopathy and isolated non-ischaemic LV scar are terms defined by left ventricular disease.
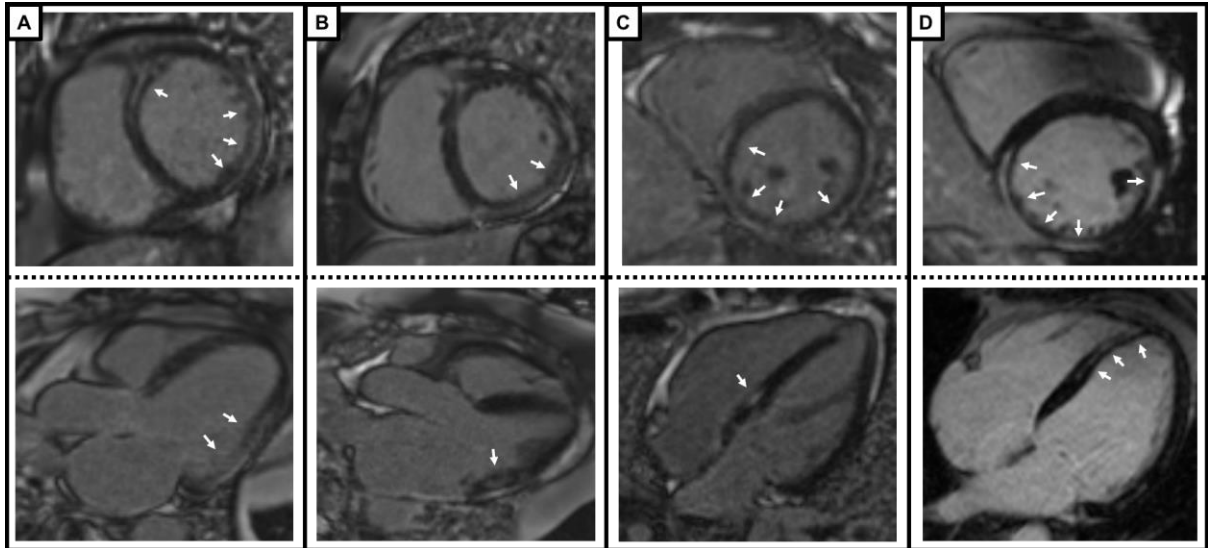
Figure 2: Magnetic resonance images from 4 patients with AC. A and B are FLNC mutation carriers whereas C and D are DSP mutation carriers. Late gadolinium enhancement (LGE) areas of the myocardium are marked with white arrows. All patients demonstrate subepicardial LGE in the inferolateral wall of the left ventricle. At a lesser degree, LGE is seen in the midwall of the intraventricular septum.
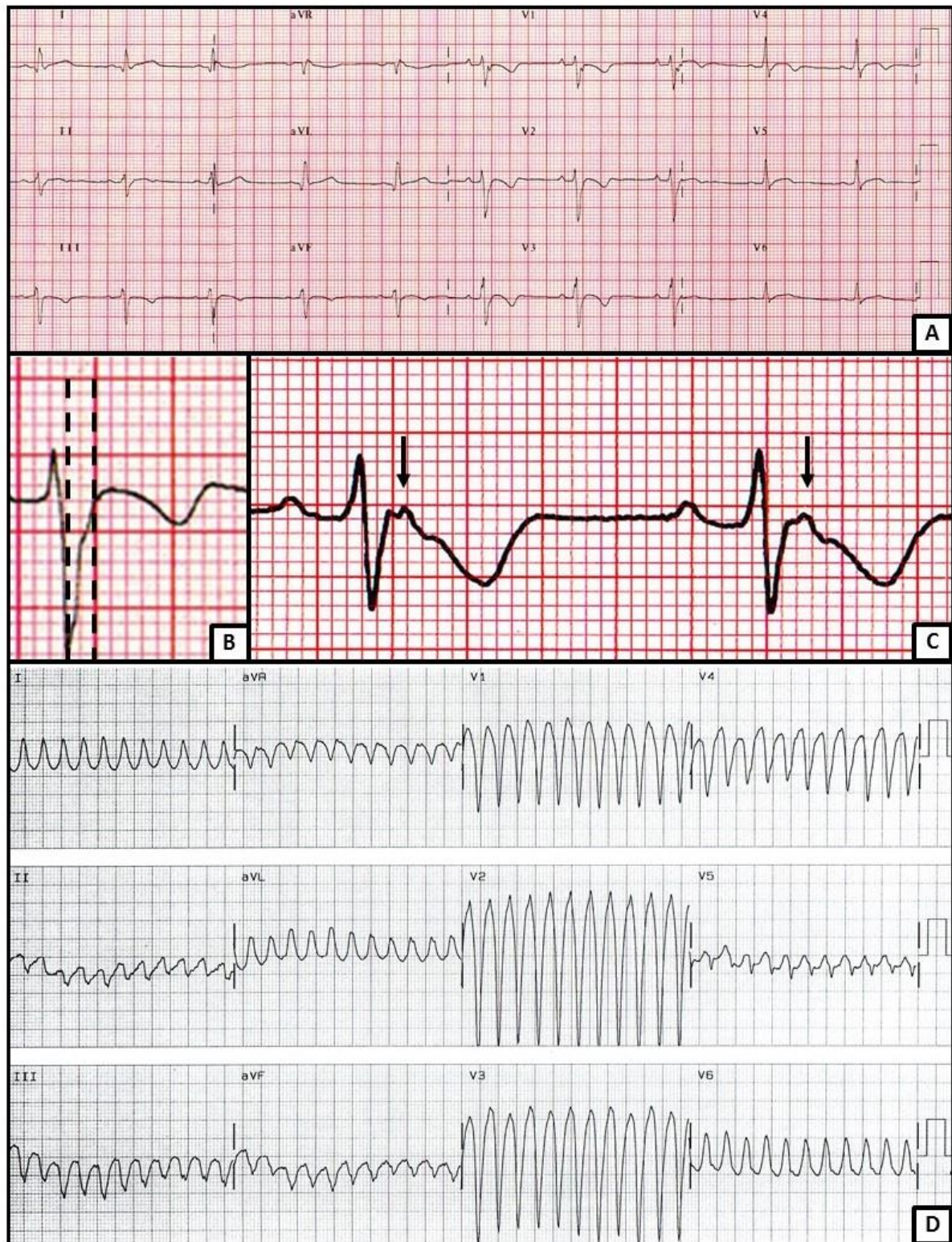
Figure 3: Typical electrocardiographic features are demonstrated from ECG recording of patients with AC including T-wave inversions in leadsV1-V3 and beyond (A), prolonged terminal activation duration (annotated between the dotted lines) more than 55 ms (B), epsilon waves (annotated by black arrows) and (C) typical ventricular tachycardia with left bundle branch block and superior axis configuration (D).
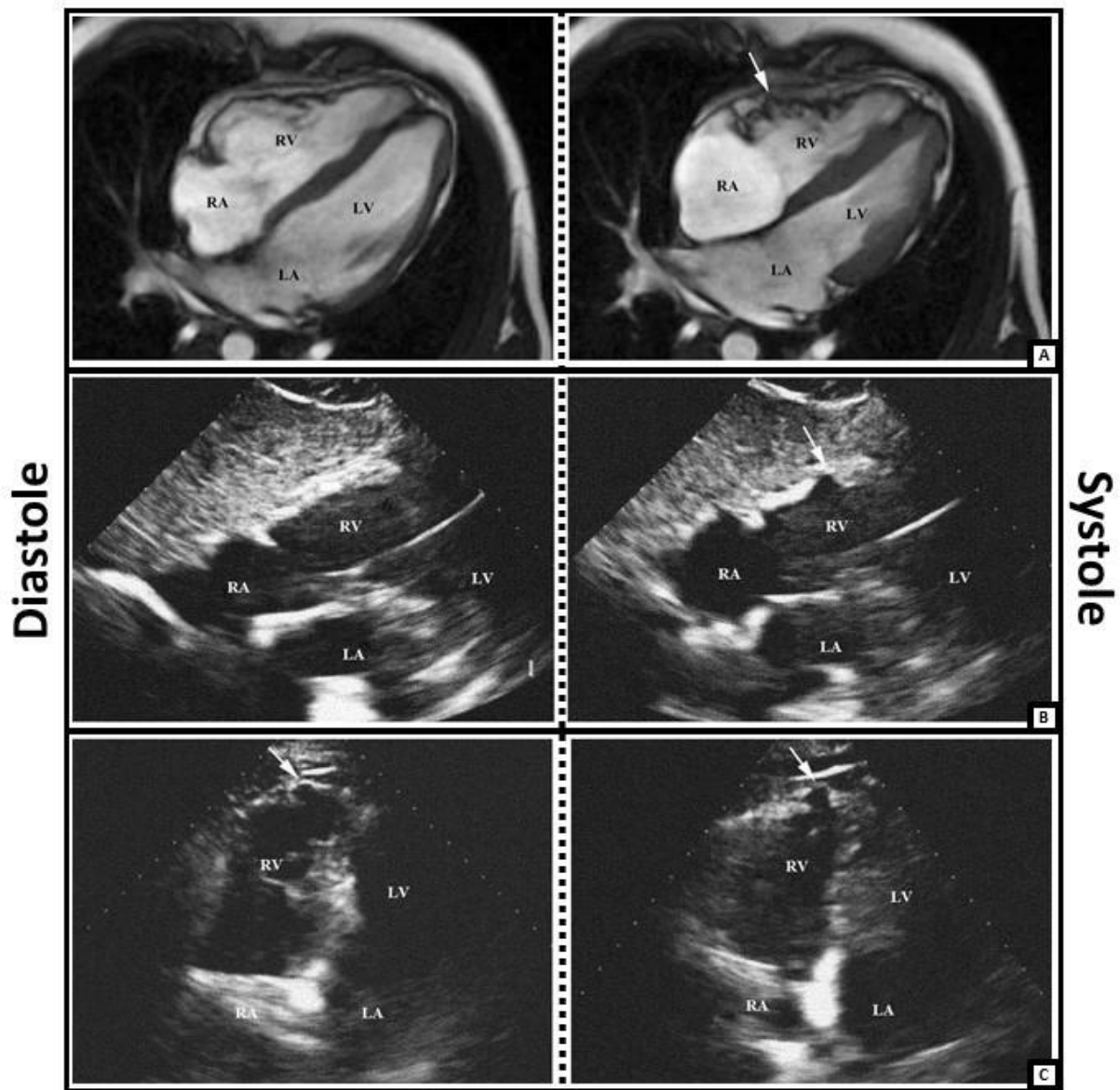
Figure 4: Imaging studies of three different AC patients with wall motion abnormalities are presented in this figure. Dotted line separates diastole (left) from systole (right). Patient A had a normal ECHO study but on cardiac magnetic resonance multiple subtle dyskinetic areas (white arrow) are noted in the right ventricular inflow tract. Typical dyskinesia for the right ventricular free wall is noted in a 2D-echocardiographic subcostal view in patient B. Patient C echocardiographic study demonstrates among others an apical aneurysm (seen both in diastole and systole) as seen in this modified four chamber apical view. LA=left atrium; LV=left ventricle; RA=right atrium; RV=right ventricle.
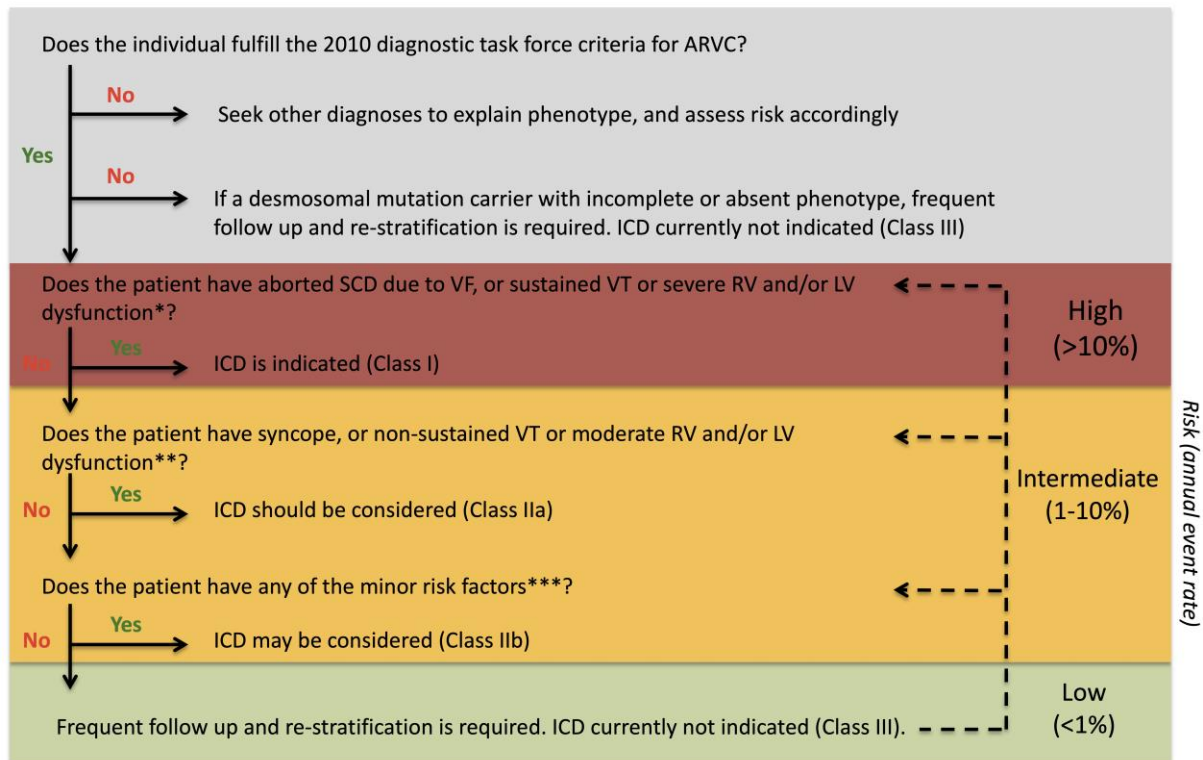
Figure 5: This diagram demonstrates the approach to the risk stratification of patients with AC or their mutation positive family members, based on the International Task Force consensus[79]. Based on the annual arrhythmic event rate of more than 10%, between 1 and 10% and less than 10% the high, intermediate and low risk groups are defined. * Severe right ventricular and/or left ventricular dysfunction is defined as RV fractional area change ≤17%, or RV ejection fraction≤35%, LV ejection fraction ≤35%. ** Moderate left or right ventricular dysfunction is defined as RV fractional area change between 24 and 17% or RV ejection fraction between 40 and 36% or LV ejection fraction between 45 and 36%. *** Minor risk factors defined in text. ARVC=Arrhythmogenic right ventricular cardiomyopathy; ICD=Intracardiac cardioverter defibrillator.

References

1. Marcus FI, Fontaine GH, Guiraudon G, et al. Right ventricular dysplasia: a report of 24 adult cases. *Circulation* 1982;65(2):384-98. [published Online First: 1982/02/01]
2. Thiene G, Nava A, Corrado D, et al. Right ventricular cardiomyopathy and sudden death in young people. *N Engl J Med* 1988;318(3):129-33. doi: 10.1056/NEJM198801213180301 [published Online First: 1988/01/21]
3. Thiene G, Basso C. Arrhythmogenic right ventricular cardiomyopathy: An update. *Cardiovascular pathology : the official journal of the Society for Cardiovascular Pathology* 2001;10(3):109-17.
4. McKenna WJ, Thiene G, Nava A, et al. Diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Task Force of the Working Group Myocardial and Pericardial Disease of the European Society of Cardiology and of the Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology. *Br Heart J* 1994;71(3):215-8. [published Online First: 1994/03/01]
5. Sen-Chowdhry S, Syrris P, Ward D, et al. Clinical and genetic characterization of families with arrhythmogenic right ventricular dysplasia/cardiomyopathy provides novel insights into patterns of disease expression. *Circulation* 2007;115(13):1710-20. doi: 10.1161/CIRCULATIONAHA.106.660241 [published Online First: 2007/03/21]
6. Marcus FI, McKenna WJ, Sherrill D, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the Task Force Criteria. *European heart journal* 2010;31(7):806-14. doi: 10.1093/eurheartj/ehq025
7. Nava A, Thiene G, Canciani B, et al. Familial occurrence of right ventricular dysplasia: a study involving nine families. *Journal of the American College of Cardiology* 1988;12(5):1222-8. [published Online First: 1988/11/01]
8. Pinto YM, Elliott PM, Arbustini E, et al. Proposal for a revised definition of dilated cardiomyopathy, hypokinetic non-dilated cardiomyopathy, and its implications for clinical practice: a position statement of the ESC working group on myocardial and pericardial diseases. *European heart journal* 2016;37(23):1850-8. doi: 10.1093/eurheartj/ehv727 [published Online First: 2016/01/23]
9. Spezzacatene A, Sinagra G, Merlo M, et al. Arrhythmogenic Phenotype in Dilated Cardiomyopathy: Natural History and Predictors of Life-Threatening Arrhythmias. *J Am Heart Assoc* 2015;4(10):e002149. doi: 10.1161/JAHA.115.002149 [published Online First: 2015/10/18]
10. Protonotarios N, Tsatsopoulou A, Patsourakos P, et al. Cardiac abnormalities in familial palmoplantar keratosis. *Br Heart J* 1986;56(4):321-6. [published Online First: 1986/10/01]
11. McKoy G, Protonotarios N, Crosby A, et al. Identification of a deletion in plakoglobin in arrhythmogenic right ventricular cardiomyopathy with palmoplantar keratoderma and woolly hair (Naxos disease). *Lancet* 2000;355(9221):2119-24. doi: 10.1016/S0140-6736(00)02379-5 [published Online First: 2000/07/21]
12. Protonotarios N, Tsatsopoulou A. Naxos disease and Carvajal syndrome: cardiocutaneous disorders that highlight the pathogenesis and broaden the spectrum of arrhythmogenic right ventricular cardiomyopathy. *Cardiovasc Pathol* 2004;13(4):185-94. doi: 10.1016/j.carpath.2004.03.609 [published Online First: 2004/06/24]
13. Rampazzo A, Nava A, Malacrida S, et al. Mutation in human desmoplakin domain binding to plakoglobin causes a dominant form of arrhythmogenic right ventricular cardiomyopathy. *Am J Hum Genet* 2002;71(5):1200-6. doi: 10.1086/344208 [published Online First: 2002/10/10]
14. Norgett EE, Hatsell SJ, Carvajal-Huerta L, et al. Recessive mutation in desmoplakin disrupts desmoplakin-intermediate filament interactions and causes dilated cardiomyopathy, woolly hair and keratoderma. *Hum Mol Genet* 2000;9(18):2761-6. [published Online First: 2000/11/07]

15. Gerull B, Heuser A, Wichter T, et al. Mutations in the desmosomal protein plakophilin-2 are common in arrhythmogenic right ventricular cardiomyopathy. *Nat Genet* 2004;36(11):1162-4. doi: 10.1038/ng1461 [published Online First: 2004/10/19]

16. Syrris P, Ward D, Asimaki A, et al. Clinical expression of plakophilin-2 mutations in familial arrhythmogenic right ventricular cardiomyopathy. *Circulation* 2006;113(3):356-64. doi: 10.1161/CIRCULATIONAHA.105.561654

17. Pilichou K, Nava A, Basso C, et al. Mutations in desmoglein-2 gene are associated with arrhythmogenic right ventricular cardiomyopathy. *Circulation* 2006;113(9):1171-9. doi: 10.1161/CIRCULATIONAHA.105.583674 [published Online First: 2006/03/01]

18. Syrris P, Ward D, Evans A, et al. Arrhythmogenic right ventricular dysplasia/cardiomyopathy associated with mutations in the desmosomal gene desmocollin-2. *Am J Hum Genet* 2006;79(5):978-84. doi: 10.1086/509122 [published Online First: 2006/10/13]

19. Asimaki A, Syrris P, Wichter T, et al. A novel dominant mutation in plakoglobin causes arrhythmogenic right ventricular cardiomyopathy. *Am J Hum Genet* 2007;81(5):964-73. doi: 10.1086/521633 [published Online First: 2007/10/10]

20. Kirchner F, Schuetz A, Boldt LH, et al. Molecular insights into arrhythmogenic right ventricular cardiomyopathy caused by plakophilin-2 missense mutations. *Circulation Cardiovascular genetics* 2012;5(4):400-11. doi: 10.1161/CIRCGENETICS.111.961854 [published Online First: 2012/07/12]

21. Pilichou K, Thiene G, Bauce B, et al. Arrhythmogenic cardiomyopathy. *Orphanet J Rare Dis* 2016;11:33. doi: 10.1186/s13023-016-0407-1 [published Online First: 2016/04/04]

22. Campuzano O, Alcalde M, Allegue C, et al. Genetics of arrhythmogenic right ventricular cardiomyopathy. *J Med Genet* 2013;50(5):280-9. doi: 10.1136/jmedgenet-2013-101523 [published Online First: 2013/03/08]

23. Kottke MD, Delva E, Kowalczyk AP. The desmosome: cell science lessons from human diseases. *Journal of cell science* 2006;119(Pt 5):797-806. doi: 10.1242/jcs.02888

24. Levin J, Bulst S, Thirion C, et al. Divergent molecular effects of desmin mutations on protein assembly in myofibrillar myopathy. *J Neuropathol Exp Neurol* 2010;69(4):415-24. doi: 10.1097/NEN.0b013e3181d71305 [published Online First: 2010/05/08]

25. Christensen AH, Andersen CB, Tybjaerg-Hansen A, et al. Mutation analysis and evaluation of the cardiac localization of TMEM43 in arrhythmogenic right ventricular cardiomyopathy. *Clin Genet* 2011;80(3):256-64. doi: 10.1111/j.1399-0004.2011.01623.x [published Online First: 2011/01/11]

26. Hodgkinson KA, Parfrey PS, Bassett AS, et al. The impact of implantable cardioverter-defibrillator therapy on survival in autosomal-dominant arrhythmogenic right ventricular cardiomyopathy (ARVD5). *Journal of the American College of Cardiology* 2005;45(3):400-8. doi: 10.1016/j.jacc.2004.08.068 [published Online First: 2005/02/01]

27. Quarta G, Syrris P, Ashworth M, et al. Mutations in the Lamin A/C gene mimic arrhythmogenic right ventricular cardiomyopathy. *European heart journal* 2012;33(9):1128-36. doi: 10.1093/eurheartj/ehr451 [published Online First: 2011/12/27]

28. Taylor M, Graw S, Sinagra G, et al. Genetic variation in titin in arrhythmogenic right ventricular cardiomyopathy-overlap syndromes. *Circulation* 2011;124(8):876-85. doi: 10.1161/CIRCULATIONAHA.110.005405 [published Online First: 2011/08/04]

29. van der Zwaag PA, van Rijsingen IA, Asimaki A, et al. Phospholamban R14del mutation in patients diagnosed with dilated cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy: evidence supporting the concept of arrhythmogenic cardiomyopathy. *Eur J Heart Fail* 2012;14(11):1199-207. doi: 10.1093/eurjhf/hfs119 [published Online First: 2012/07/24]

30. Ortiz-Genga MF, Cuenca S, Dal Ferro M, et al. Truncating FLNC Mutations Are Associated With High-Risk Dilated and Arrhythmogenic Cardiomyopathies. *Journal of the American College of Cardiology* 2016;68(22):2440-51. doi: 10.1016/j.jacc.2016.09.927

31. Te Riele AS, Agullo-Pascual E, James CA, et al. Multilevel analyses of SCN5A mutations in arrhythmogenic right ventricular dysplasia/cardiomyopathy suggest non-canonical mechanisms for disease pathogenesis. *Cardiovasc Res* 2017;113(1):102-11. doi: 10.1093/cvr/cvw234 [published Online First: 2017/01/11]

32. Cerrone M, Noorman M, Lin X, et al. Sodium current deficit and arrhythmogenesis in a murine model of plakophilin-2 haploinsufficiency. *Cardiovasc Res* 2012;95(4):460-8. doi: 10.1093/cvr/cvs218 [published Online First: 2012/07/06]

33. Rizzo S, Lodder EM, Verkerk AO, et al. Intercalated disc abnormalities, reduced Na(+) current density, and conduction slowing in desmoglein-2 mutant mice prior to cardiomyopathic changes. *Cardiovasc Res* 2012;95(4):409-18. doi: 10.1093/cvr/cvs219 [published Online First: 2012/07/06]

34. van Hengel J, Calore M, Bauce B, et al. Mutations in the area composita protein alphaT-catenin are associated with arrhythmogenic right ventricular cardiomyopathy. *European heart journal* 2013;34(3):201-10. doi: 10.1093/eurheartj/ehs373 [published Online First: 2012/11/09]

35. Mayosi BM, Fish M, Shaboodien G, et al. Identification of Cadherin 2 (CDH2) Mutations in Arrhythmogenic Right Ventricular Cardiomyopathy. *Circulation Cardiovascular genetics* 2017;10(2) doi: 10.1161/CIRCGENETICS.116.001605 [published Online First: 2017/03/11]

36. Bauce B, Basso C, Rampazzo A, et al. Clinical profile of four families with arrhythmogenic right ventricular cardiomyopathy caused by dominant desmoplakin mutations. *European heart journal* 2005;26(16):1666-75. doi: 10.1093/eurheartj/ehi341

37. Lopez-Ayala JM, Pastor-Quirante F, Gonzalez-Carrillo J, et al. Genetics of myocarditis in arrhythmogenic right ventricular dysplasia. *Heart rhythm : the official journal of the Heart Rhythm Society* 2015;12(4):766-73. doi: 10.1016/j.hrthm.2015.01.001

38. Mavrogeni S, Protonotarios N, Tsatsopoulou A, et al. Naxos disease evolution mimicking acute myocarditis: the role of cardiovascular magnetic resonance imaging. *International journal of cardiology* 2013;166(1):e14-5. doi: 10.1016/j.ijcard.2012.12.078

39. Pilichou K, Remme CA, Basso C, et al. Myocyte necrosis underlies progressive myocardial dystrophy in mouse dsg2-related arrhythmogenic right ventricular cardiomyopathy. *The Journal of experimental medicine* 2009;206(8):1787-802. doi: 10.1084/jem.20090641 [published Online First: 2009/07/29]

40. Miani D, Pinamonti B, Bussani R, et al. Right ventricular dysplasia: a clinical and pathological study of two families with left ventricular involvement. *British heart journal* 1993;69(2):151-7.

41. Pinamonti B, Miani D, Sinagra G, et al. Familial right ventricular dysplasia with biventricular involvement and inflammatory infiltration. Heart Muscle Disease Study Group. *Heart* 1996;76(1):66-9.

42. Alcalai R, Metzger S, Rosenheck S, et al. A recessive mutation in desmoplakin causes arrhythmogenic right ventricular dysplasia, skin disorder, and woolly hair. *Journal of the American College of Cardiology* 2003;42(2):319-27. [published Online First: 2003/07/24]

43. Simpson MA, Mansour S, Ahnood D, et al. Homozygous mutation of desmocollin-2 in arrhythmogenic right ventricular cardiomyopathy with mild palmoplantar keratoderma and woolly hair. *Cardiology* 2009;113(1):28-34. doi: 10.1159/000165696

44. Kley RA, Hellenbroich Y, van der Ven PF, et al. Clinical and morphological phenotype of the filamin myopathy: a study of 31 German patients. *Brain* 2007;130(Pt 12):3250-64. doi: 10.1093/brain/awm271 [published Online First: 2007/12/07]

45. Dalakas MC, Park KY, Semino-Mora C, et al. Desmin myopathy, a skeletal myopathy with cardiomyopathy caused by mutations in the desmin gene. *N Engl J Med* 2000;342(11):770-80. doi: 10.1056/NEJM200003163421104 [published Online First: 2000/03/16]

46. Berte B, Denis A, Amraoui S, et al. Characterization of the Left-Sided Substrate in Arrhythmogenic Right Ventricular Cardiomyopathy. *Circulation Arrhythmia and electrophysiology* 2015;8(6):1403-12. doi: 10.1161/CIRCEP.115.003213 [published Online First: 2015/08/28]

47. Camm CF, Tichnell C, James CA, et al. Premature ventricular contraction variability in arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Journal of cardiovascular electrophysiology* 2015;26(1):53-7. doi: 10.1111/jce.12544 [published Online First: 2014/09/13]

48. Bhonsale A, James CA, Tichnell C, et al. Risk stratification in arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated desmosomal mutation carriers. *Circulation Arrhythmia and electrophysiology* 2013;6(3):569-78. doi: 10.1161/CIRCEP.113.000233 [published Online First: 2013/05/15]

49. Kaplan SR, Gard JJ, Protonotarios N, et al. Remodeling of myocyte gap junctions in arrhythmogenic right ventricular cardiomyopathy due to a deletion in plakoglobin (Naxos disease). *Heart rhythm : the official journal of the Heart Rhythm Society* 2004;1(1):3-11. doi: 10.1016/j.hrthm.2004.01.001 [published Online First: 2005/04/27]

50. Link MS, Laidlaw D, Polonsky B, et al. Ventricular arrhythmias in the North American multidisciplinary study of ARVC: predictors, characteristics, and treatment. *Journal of the American College of Cardiology* 2014;64(2):119-25. doi: 10.1016/j.jacc.2014.04.035 [published Online First: 2014/07/12]

51. Cox MG, Nelen MR, Wilde AA, et al. Activation delay and VT parameters in arrhythmogenic right ventricular dysplasia/cardiomyopathy: toward improvement of diagnostic ECG criteria. *Journal of cardiovascular electrophysiology* 2008;19(8):775-81. doi: 10.1111/j.1540-8167.2008.01140.x

52. Hoffmayer KS, Bhave PD, Marcus GM, et al. An electrocardiographic scoring system for distinguishing right ventricular outflow tract arrhythmias in patients with arrhythmogenic right ventricular cardiomyopathy from idiopathic ventricular tachycardia. *Heart rhythm : the official journal of the Heart Rhythm Society* 2013;10(4):477-82. doi: 10.1016/j.hrthm.2012.12.009 [published Online First: 2012/12/19]

53. Basso C, Thiene G, Corrado D, et al. Arrhythmogenic right ventricular cardiomyopathy. Dysplasia, dystrophy, or myocarditis? *Circulation* 1996;94(5):983-91.

54. Basso C, Corrado D, Marcus FI, et al. Arrhythmogenic right ventricular cardiomyopathy. *Lancet* 2009;373(9671):1289-300. doi: 10.1016/S0140-6736(09)60256-7

55. Zorzi A, Migliore F, Elmaghawry M, et al. Electrocardiographic predictors of electroanatomic scar size in arrhythmogenic right ventricular cardiomyopathy: implications for arrhythmic risk stratification. *Journal of cardiovascular electrophysiology* 2013;24(12):1321-7. doi: 10.1111/jce.12246

56. Sen-Chowdhry S, Syrris P, Prasad SK, et al. Left-dominant arrhythmogenic cardiomyopathy: an under-recognized clinical entity. *Journal of the American College of Cardiology* 2008;52(25):2175-87. doi: 10.1016/j.jacc.2008.09.019 [published Online First: 2008/12/20]

57. Protonotarios A, Anastasakis A, Panagiotakos DB, et al. Arrhythmic risk assessment in genotyped families with arrhythmogenic right ventricular cardiomyopathy. *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology* 2016;18(4):610-6. doi: 10.1093/europace/euv061 [published Online First: 2015/04/01]

58. Jain R, Dalal D, Daly A, et al. Electrocardiographic features of arrhythmogenic right ventricular dysplasia. *Circulation* 2009;120(6):477-87. doi: 10.1161/CIRCULATIONAHA.108.838821

59. Protonotarios A, Anastasakis A, Tsatsopoulou A, et al. Clinical Significance of Epsilon Waves in Arrhythmogenic Cardiomyopathy. *Journal of cardiovascular electrophysiology* 2015 doi: 10.1111/jce.12755

60. Platonov PG, Calkins H, Hauer RN, et al. High interobserver variability in the assessment of epsilon waves: Implications for diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia. *Heart rhythm : the official journal of the Heart Rhythm Society* 2016;13(1):208-16. doi: 10.1016/j.hrthm.2015.08.031

61. Leclercq JF, Coumel P. Late potentials in arrhythmogenic right ventricular dysplasia. Prevalence, diagnostic and prognostic values. *European heart journal* 1993;14 Suppl E:80-3.

62. Corrado D, Basso C, Leoni L, et al. Three-dimensional electroanatomic voltage mapping increases accuracy of diagnosing arrhythmogenic right ventricular cardiomyopathy/dysplasia. *Circulation* 2005;111(23):3042-50. doi: 10.1161/CIRCULATIONAHA.104.486977

63. Migliore F, Zorzi A, Silvano M, et al. Prognostic value of endocardial voltage mapping in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia. *Circulation Arrhythmia and electrophysiology* 2013;6(1):167-76. doi: 10.1161/CIRCEP.111.974881 [published Online First: 2013/02/09]

64. Philips B, te Riele AS, Sawant A, et al. Outcomes and ventricular tachycardia recurrence characteristics after epicardial ablation of ventricular tachycardia in arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Heart rhythm : the official journal of the Heart Rhythm Society* 2015;12(4):716-25. doi: 10.1016/j.hrthm.2014.12.018 [published Online First: 2014/12/23]

65. Kimura Y, Noda T, Matsuyama TA, et al. Heart failure in patients with arrhythmogenic right ventricular cardiomyopathy: What are the risk factors? *International journal of cardiology* 2017;241:288-94. doi: 10.1016/j.ijcard.2017.04.061 [published Online First: 2017/05/04]

66. van Tintelen JP, Van Gelder IC, Asimaki A, et al. Severe cardiac phenotype with right ventricular predominance in a large cohort of patients with a single missense mutation in the DES gene. *Heart rhythm : the official journal of the Heart Rhythm Society* 2009;6(11):1574-83. doi: 10.1016/j.hrthm.2009.07.041 [published Online First: 2009/11/03]

67. Kato K, Takahashi N, Fujii Y, et al. LMNA cardiomyopathy detected in Japanese arrhythmogenic right ventricular cardiomyopathy cohort. *J Cardiol* 2016;68(4):346-51. doi: 10.1016/j.jjcc.2015.10.013 [published Online First: 2015/12/02]

68. Brun F, Barnes CV, Sinagra G, et al. Titin and desmosomal genes in the natural history of arrhythmogenic right ventricular cardiomyopathy. *Journal of medical genetics* 2014;51(10):669-76. doi: 10.1136/jmedgenet-2014-102591

69. Te Riele AS, James CA, Philips B, et al. Mutation-positive arrhythmogenic right ventricular dysplasia/cardiomyopathy: the triangle of dysplasia displaced. *Journal of cardiovascular electrophysiology* 2013;24(12):1311-20. doi: 10.1111/jce.12222

70. Philips B, Madhavan S, James CA, et al. Arrhythmogenic right ventricular dysplasia/cardiomyopathy and cardiac sarcoidosis: distinguishing features when the diagnosis is unclear. *Circulation Arrhythmia and electrophysiology* 2014;7(2):230-6. doi: 10.1161/CIRCEP.113.000932 [published Online First: 2014/03/04]

71. James CA, Bhonsale A, Tichnell C, et al. Exercise increases age-related penetrance and arrhythmic risk in arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated desmosomal mutation carriers. *Journal of the American College of Cardiology* 2013;62(14):1290-97. doi: 10.1016/j.jacc.2013.06.033 [published Online First: 2013/07/23]

72. Sawant AC, Bhonsale A, te Riele AS, et al. Exercise has a disproportionate role in the pathogenesis of arrhythmogenic right ventricular dysplasia/cardiomyopathy in patients without desmosomal mutations. *Journal of the American Heart Association* 2014;3(6):e001471. doi: 10.1161/JAHA.114.001471

73. Ruwald AC, Marcus F, Estes NA, 3rd, et al. Association of competitive and recreational sport participation with cardiac events in patients with arrhythmogenic right ventricular cardiomyopathy: results from the North American multidisciplinary study of arrhythmogenic right ventricular cardiomyopathy. *European heart journal* 2015;36(27):1735-43. doi: 10.1093/eurheartj/ehv110 [published Online First: 2015/04/22]

74. Wang W, Orgeron G, Tichnell C, et al. Impact of Exercise Restriction on Arrhythmic Risk Among Patients With Arrhythmogenic Right Ventricular Cardiomyopathy. *J Am Heart Assoc* 2018;7(12) doi: 10.1161/JAHA.118.008843 [published Online First: 2018/06/18]

75. Wichter T, Borggrefe M, Haverkamp W, et al. Efficacy of antiarrhythmic drugs in patients with arrhythmogenic right ventricular disease. Results in patients with inducible and noninducible ventricular tachycardia. *Circulation* 1992;86(1):29-37. [published Online First: 1992/07/01]

76. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *European heart journal* 2016;37(27):2129-200. doi: 10.1093/eurheartj/ehw128

77. Wlodarska EK, Wozniak O, Konka M, et al. Thromboembolic complications in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology* 2006;8(8):596-600. doi: 10.1093/europace/eul053 [published Online First: 2006/06/09]

78. van Rijsingen IA, Bakker A, Azim D, et al. Lamin A/C mutation is independently associated with an increased risk of arterial and venous thromboembolic complications. *International journal of cardiology* 2013;168(1):472-7. doi: 10.1016/j.ijcard.2012.09.118 [published Online First: 2012/10/18]

79. Corrado D, Wichter T, Link MS, et al. Treatment of arrhythmogenic right ventricular cardiomyopathy/dysplasia: an international task force consensus statement. *European heart journal* 2015;36(46):3227-37. doi: 10.1093/eurheartj/ehv162 [published Online First: 2015/07/29]

80. Tandri H, Saranathan M, Rodriguez ER, et al. Noninvasive detection of myocardial fibrosis in arrhythmogenic right ventricular cardiomyopathy using delayed-enhancement magnetic resonance imaging. *Journal of the American College of Cardiology* 2005;45(1):98-103. doi: 10.1016/j.jacc.2004.09.053 [published Online First: 2005/01/05]

81. Garcia FC, Bazan V, Zado ES, et al. Epicardial substrate and outcome with epicardial ablation of ventricular tachycardia in arrhythmogenic right ventricular cardiomyopathy/dysplasia. *Circulation* 2009;120(5):366-75. doi: 10.1161/CIRCULATIONAHA.108.834903 [published Online First: 2009/07/22]

82. Bhonsale A, Groeneweg JA, James CA, et al. Impact of genotype on clinical course in arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated mutation carriers. *European heart journal* 2015;36(14):847-55. doi: 10.1093/eurheartj/ehu509 [published Online First: 2015/01/27]

83. Bhonsale A, James CA, Tichnell C, et al. Incidence and predictors of implantable cardioverter-defibrillator therapy in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy undergoing implantable cardioverter-defibrillator implantation for primary prevention. *Journal of the American College of Cardiology* 2011;58(14):1485-96. doi: 10.1016/j.jacc.2011.06.043 [published Online First: 2011/09/24]

84. Wichter T, Paul M, Wollmann C, et al. Implantable cardioverter/defibrillator therapy in arrhythmogenic right ventricular cardiomyopathy: single-center experience of long-term follow-up and complications in 60 patients. *Circulation* 2004;109(12):1503-8. doi: 10.1161/01.CIR.0000121738.88273.43 [published Online First: 2004/03/10]

85. Rigato I, Bauce B, Rampazzo A, et al. Compound and digenic heterozygosity predicts lifetime arrhythmic outcome and sudden cardiac death in desmosomal gene-related arrhythmogenic right ventricular cardiomyopathy. *Circulation Cardiovascular genetics* 2013;6(6):533-42. doi: 10.1161/CIRCGENETICS.113.000288 [published Online First: 2013/09/28]

86. Saguner AM, Medeiros-Domingo A, Schwyzer MA, et al. Usefulness of inducible ventricular tachycardia to predict long-term adverse outcomes in arrhythmogenic right ventricular cardiomyopathy. *Am J Cardiol* 2013;111(2):250-7. doi: 10.1016/j.amjcard.2012.09.025 [published Online First: 2012/10/30]

87. Santangeli P, Dello Russo A, Pieroni M, et al. Fragmented and delayed electrograms within fibrofatty scar predict arrhythmic events in arrhythmogenic right ventricular cardiomyopathy: results from a prospective risk stratification study. *Heart rhythm : the official journal of the Heart Rhythm Society* 2012;9(8):1200-6. doi: 10.1016/j.hrthm.2012.03.057 [published Online First: 2012/04/03]

88. Saguner AM, Ganahl S, Baldinger SH, et al. Usefulness of electrocardiographic parameters for risk prediction in arrhythmogenic right ventricular dysplasia. *Am J Cardiol* 2014;113(10):1728-34. doi: 10.1016/j.amjcard.2014.02.031 [published Online First: 2014/05/06]

89. te Riele AS, James CA, Rastegar N, et al. Yield of serial evaluation in at-risk family members of patients with ARVD/C. *Journal of the American College of Cardiology* 2014;64(3):293-301. doi: 10.1016/j.jacc.2014.04.044 [published Online First: 2014/07/19]

90. Kies P, Bootsma M, Bax JJ, et al. Serial reevaluation for ARVD/C is indicated in patients presenting with left bundle branch block ventricular tachycardia and minor ECG abnormalities. *Journal of cardiovascular electrophysiology* 2006;17(6):586-93. doi: 10.1111/j.1540-8167.2006.00442.x [published Online First: 2006/07/14]

91. Groeneweg JA, Bhonsale A, James CA, et al. Clinical Presentation, Long-Term Follow-Up, and Outcomes of 1001 Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy Patients and Family Members. *Circulation Cardiovascular genetics* 2015;8(3):437-46. doi: 10.1161/CIRCGENETICS.114.001003