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Arrhythmogenic right ventricular cardiomyopathy

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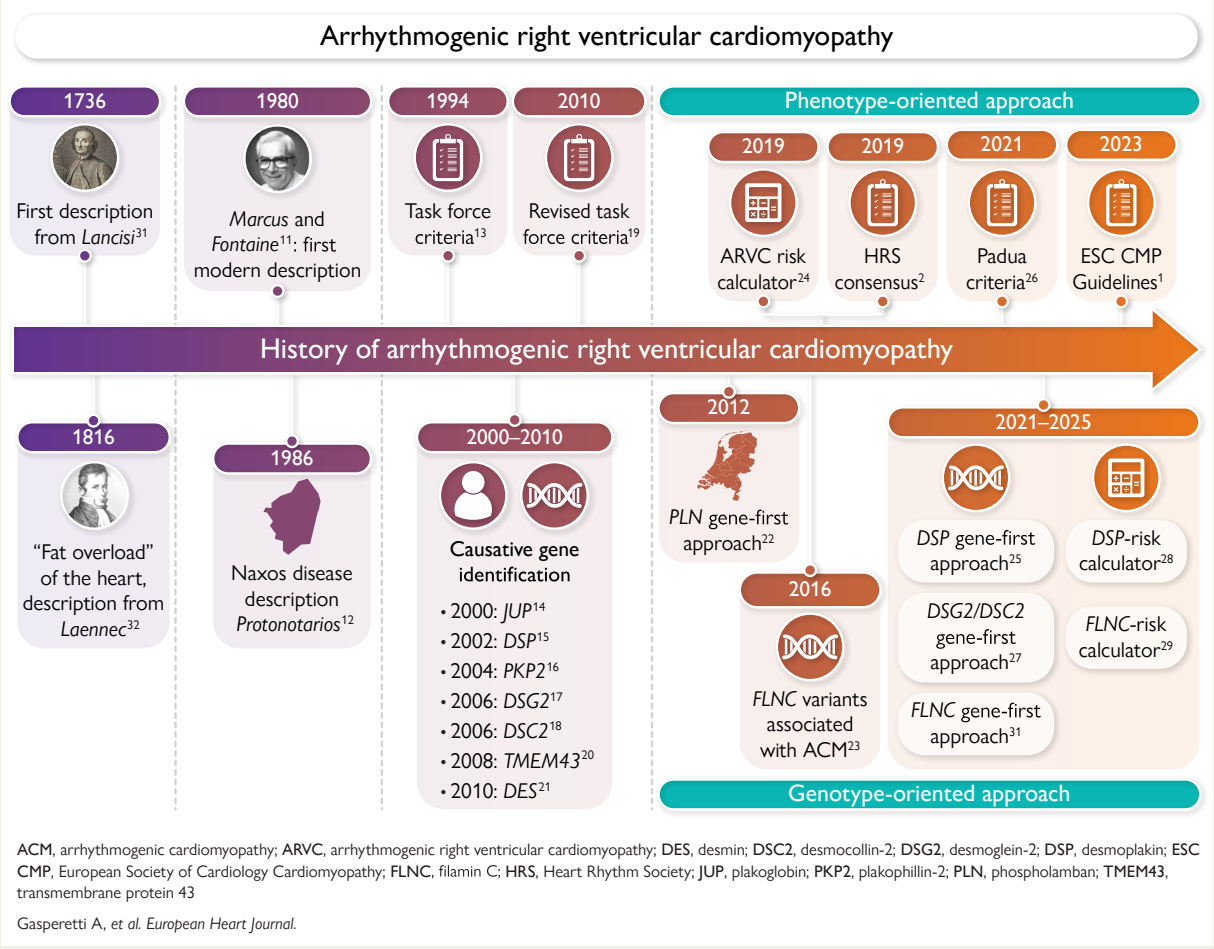
Graphical Abstract



Evolution of arrhythmogenic cardiomyopathy approaches over time. Timeline of main descriptions and discoveries pertinent to ARVC/ACM.

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Abstract

Arrhythmogenic cardiomyopathy (ACM) is a form of inheritable cardiomyopathy characterized by ventricular scarring and/or fibro-fatty replacement. ACM is associated with a significant risk of sudden cardiac death due to ventricular arrhythmias, especially in young patients and endurance athletes. Aim of this review is to summarize the changing in understanding and framing of this multi-faceted disease, in particular highlighting the current transition from a phenotype-first to a genotype-first framework for diagnosis and management.

Keywords Arrhythmogenic right ventricular cardiomyopathy • Arrhythmogenic cardiomyopathy • Desmosomal • Sudden cardiac death

Introduction

Arrhythmogenic cardiomyopathy (ACM) is a form of inheritable cardiomyopathy characterized by ventricular scarring and/or fibro-fatty replacement.[1–3] ACM is associated with a significant risk of sudden cardiac death (SCD) due to ventricular arrhythmias (VAs), especially in young patients and endurance athletes.[4–6] Although its incidence varies extensively by geographical area due to the presence of founder variant effects, it is estimated to affect 1:2000–1:5000 individuals and to represent the most common cause of SCD during physical exercise.[4,7,8] Around 50%–60% of patients with a diagnosis of ACM will carry causative variants in one or more genes associated with this disease. The aim of this review article is to summarize the main aspects of the disease, as well as a modern approach to diagnosis and management of the classical and non-classical (left-sided) ACM phenotype, without addressing here the larger and partially overlapping non-dilated left ventricular cardiomyopathy phenotype. We will also highlight the ongoing transition from a phenotype-first to a genotype-first framework for diagnosis and management.[9,10]

Historical perspective and disease diagnosis

The definition of ACM has changed extensively over the years, following the evolving understanding of this disease by the scientific community (*Graphical Abstract*).[1,2,11–32]

The first historical description of a disease characterized by right ventricular (RV) aneurysmatic dilatation, SCD, and a familiar predisposition dates back to 1736, in the book '*De Motu Cordis et Aneurysmatibus*' by the pope physician Giovanni Maria Lancisi.[31] A century later, René Laennec added histological descriptors to this disease, reporting the presence of what he called 'fat overload' (a precursor of the term fibro-fatty infiltration) in the hearts of patients who died suddenly after physical exercise.[32] The first modern description of this disease, however, was presented in 1982 by Marcus, Fontaine, and colleagues.[11] In their manuscript, they reported a case series of 24 adult patients experiencing VAs with left bundle branch block morphology of RV origin and a cardiac pathology characterized by fibrous replacement and dilatation of the RV cavity. Subsequent histological studies from the University of Padua deeply characterized the pathological hallmarks of this disease, defining it as the presence of transmural fibro-fatty replacement in the RV wall, frequently with aneurysms.[6] These works, among many others, put the newly named arrhythmogenic RV dysplasia (ARVD) under the spotlight and led the scientific community to gather a dedicated Task Force for the development of diagnostic criteria for this disease. The original Task Force Criteria (TFC) published in 1994 were the result of that effort.[13] The genetic revolution from the early 2000s, however, led to the discovery of a clear association between pathogenic/likely pathogenic (P/LP) variants in several genes encoding desmosomal proteins and the development of a phenotype now recognized to be a cardiomyopathy (e.g. ARVD/C)[14–18] and explaining the familiar and regional clustering of disease observed. In 2010, the TFC were revised to incorporate not only clinical and morphological abnormalities (with more quantifiable cut-offs for RV dysfunction) but also genetic test results and more refined family history information.[19]

The 2010 TFC have shaped the modern understanding of ACM and are currently the only extensively validated set of diagnostic criteria available for this disease (*Table 1*).[28,29,33] They are, however, not exempt from limitations. Both the 1994 and 2010 versions of the TFC, in fact, exclusively focused on disease forms presenting with an RV phenotype. While the RV-dominant forms of ACM were the first to be described and the most easily differentiated forms of disease, wider access to cardiac magnetic resonance imaging (MRI) and progressive increase in clinicians' awareness alike led to a significant increase in recognition of biventricular as well as left ventricular (LV)-dominant forms of disease in the first and second decade of the new millennia,[34–38] especially among patients with causative variants in specific desmosomal (i.e. desmoplakin [*DSP*]) and non-desmosomal (i.e. phospolamban [*PLN*]) genes. Those findings led to the change of nomenclature from ARVD/C to the currently used term 'ACM' and forced the community to start rethink the diagnostic framing of this disease.

As a result, two major documents were published. In 2019, the Heart Rhythm Society (HRS) released an expert consensus on ACM,[2] with the aim of broadening the definition of the disease and emphasizing the importance of genetic testing. The ACM phenotype was broadly defined as 'an arrhythmogenic disorder of the myocardium not secondary to ischaemic, hypertensive, or valvular heart disease'. This consensus document emphasized the importance of genetic testing for diagnosis and management and also encompassed biventricular and left-sided genetic forms of disease. This document was also so broad in the definition of ACM that it resulted in etymological confusion as it included a large group of conditions (i.e. sarcoidosis or Chagas disease) not historically included in the ACM

Table 1 List and characteristics of genes with definite and moderate evidence associated with arrhythmogenic cardiomyopathy development

Gene	Position	Prevalence	Phenotype	Notable characteristics	Specific Gene Calculator?
PKP2	Desmosome	++++	Most commonly RV dominant	Highest susceptibility to physical exercise	No—but best performance of ARVC Risk Calculator
JUP	Desmosome	+	RV dominant or BiV	Palmo-plantar keratoderma and curly hair	No
DSP	Desmosome	+++	Most commonly BiV or LV dominant	Frequent myocarditis episodes Palmo-plantar keratoderma and curly hair Female sex potentially at higher risk	Yes[28]
DGS2	Desmosome	++	Most commonly RV dominant or BiV	High risk of HF	No
DSC2	Desmosome	+	Most commonly RV dominant or BiV		No
FLNC	Cytoskeletal	++	Most commonly LV dominant		Yes[29]
PLN R14del	Calcium Handling	+	Most commonly Biv or LV dominant	Lower susceptibility to physical exercise	Yes[33]
DES	Intermediate Filament	++	LV dominant	Commonly associated with AV conduction disturbance	No
TMEM43 S358L	Nuclear Envelope	+	Most commonly Biv or LV dominant	Very high risk of VA in males	No

DES, desmin; DSC2, desmocollin-2 DSG2, desmoglein-2; DSP, desmoplakin; FLNC, filamin C; PKP2, plakophilin-2; PLN, phospholamban; JUP, plakoglobin; TMEM43, transmembrane protein 43.

spectrum. A subsequent attempt at overcoming an 'RV-centric' paradigm of ACM was spearheaded with a new set of diagnostic criteria (the so-called Padua criteria), published in 2020,[26] later expanded by the European Task Force consensus report.[39] These criteria aimed to refine and improve the 2010 TFC, by including a specific set of criteria for the LV and biventricular forms of the disease. While this represented a bold initiative, the lack of validation and systematic testing, as well as concerns regarding their specificity, have so far prevented wide uptake in their use.

As a result of this extensive and often conflicting set of definitions and diagnostic criteria, the term ACM may be used to describe a vast spectrum of inherently different genetic and acquired disease phenotypes, with very little consensus across clinicians. Recently, data have accumulated establishing gene-specific patterns of clinical characteristics, risk factors and outcomes, that make it clear that the 'ACM' definition, regardless of the criteria used, are insufficient, for genetic forms of ACM. Thus, the scientific community has begun to move away from an initial phenotypic classification of ACM, in favour of a genotype-first-approach (see below section 'moving towards a genotype-first approach').

General management of patients with ACM

Patients with ACM usually present with a mixture of very classic (i.e. sudden cardiac arrest during endurance exercise) as well as subtle signs and symptoms (i.e. unclear pre-syncope in a young athlete, T-wave inversions in right-sided leads at electrocardiogram (ECG), palpations caused by isolated premature ventricular complexes [PVC]). As clinical suspicion is in the eyes of the beholder, ACM is an important differential diagnosis to have when evaluating young patients without classic cardiovascular risk factors. If a clinical suspicion of ACM is postulated, Holter monitors as well as advanced imaging are frequently acquired at first presentation and/or—almost often—at the time of a tertiary centre expert evaluation. *Figure 1* reports the classical ECG and cardiac magnetic resonance findings of two patients with ACM.

Given the complexity of this disease, its modern management is based on a multidisciplinary approach to this disease, involving multiple specialists (i.e. cardiac electrophysiologists, heart failure specialists, cardiac imagers, and geneticists/genetic counsellors). The clinical assessment and management of patients with ACM is based on five main clinical pillars, detailed below (*Figure 2*).

Correct diagnosis

ACM is a unique form of cardiac disease, presenting several disease-specific recommendations (i.e. sports abstinence and use of disease-specific risk calculators). A correct diagnosis is therefore the first step needed for proper clinical management. As mentioned above, several different sets of criteria exist and

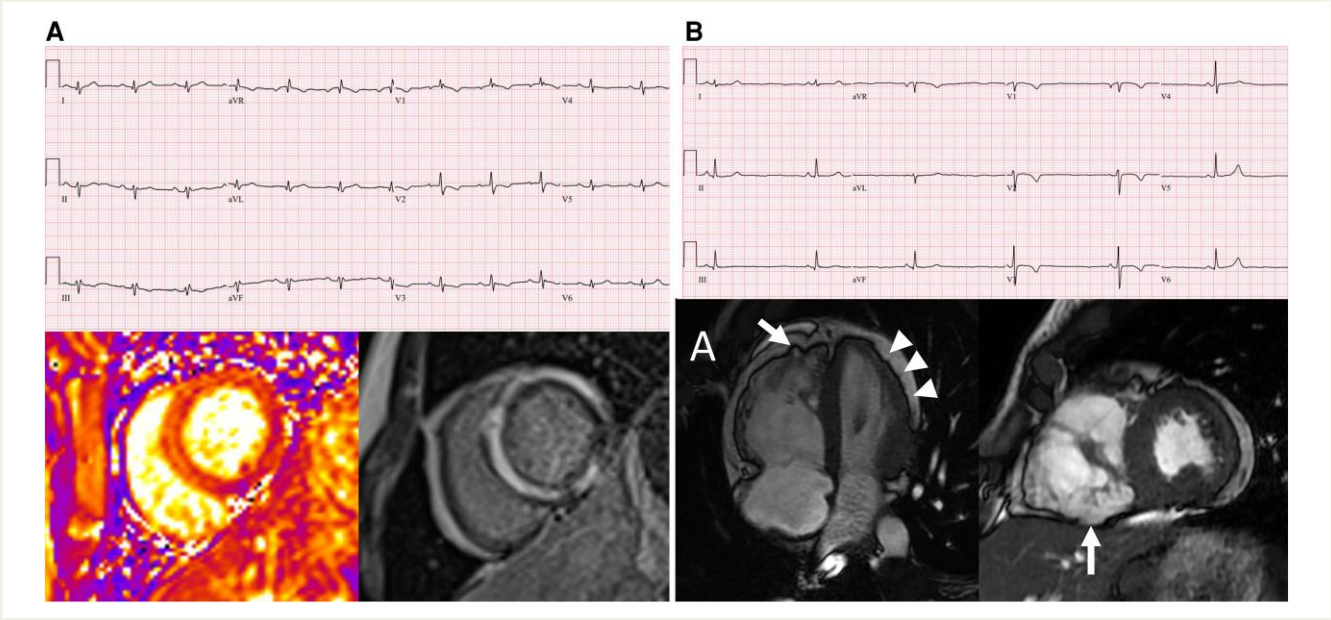

Figure 1 (*A*) 23-year-old male with left-dominant arrhythmogenic cardiomyopathy with a personal history of multiple episodes of myocarditis; originally presented with VF arrest, was found harbouring a DSP pathogenic variant. ECG is significant for incomplete RBBB, LAFB, and low voltages across the precordial leads. Left lower panel report short axis T2 mapping image shows diffusely increased T2 times in the basal LV myocardium (mean >60 ms). Right lower panel reports short axis segmented LGE image at same level showing intense ring like sub-epicardial enhancement in basal LV. (*B*) 31-year-old female with arrhythmogenic biventricular cardiomyopathy harbouring a PKP2 variant. ECG shows sinus bradycardia with deep inverted T waves in V1-V3 (major TFC criteria). Left inferior panel reports a four-chamber bright blood image showing dilated RV with microaneurysm (arrow) and subepicardial fatty infiltration of the LV apical-lateral wall (arrowheads). Right inferior panel reports short axis bright blood cine image obtained in systole showing focal dyskinesia in the mid RV inferior wall

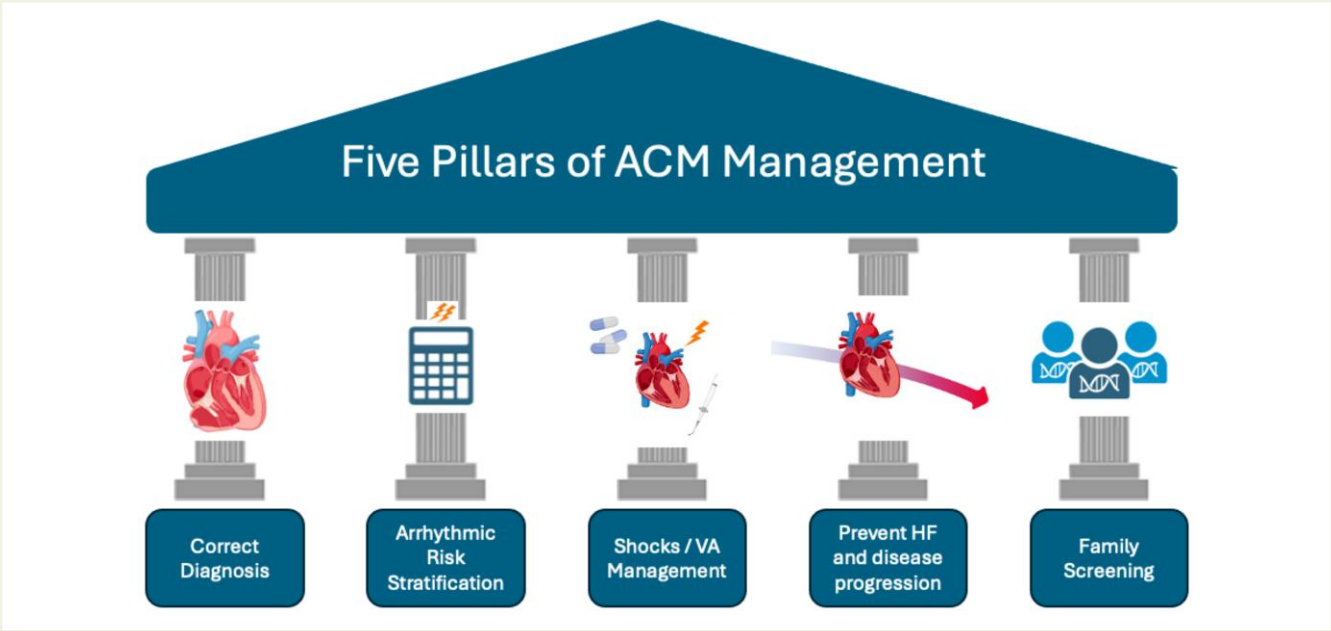

Figure 2 Graphical representation of the five pillars of arrhythmogenic cardiomyopathy management. HF, heart failure; VA, ventricular arrhythmia

have been used in the scientific literature (*Table 2*).[13,19,26] Regardless of the diagnostic criteria used, however, a final diagnosis is often not so easy to achieve, as a significant diagnostic overlap between ACM and several other forms of cardiac pathology clearly exist. Indeed, over the years numerous studies have reported patients with biopsy-proven myocarditis, cardiac sarcoidosis, or endurance athletes with no underlying pathology as example of 'disease' phenocopies, as these conditions may not infrequently fulfil diagnostic criteria for ACM.[5,40–44] Additionally, in light of its significant disease burden, a suspicion of ACM may not infrequently be invoked in cases of idiopathic RV outflow tract (RVOT) ventricular tachycardia or cardiac syncope.[45]

Hence, the job of the expert clinician is to be able to see through the smoke of phenocopies to identify the true cases of ACM. Most of this diagnostic challenge is due by the significant intra-operator variability in the reads and interpretation of several diagnostic tests, where calling (or not calling) the presence of subtle finding can significantly impact on the overall diagnostic score (and therefore final diagnosis) of a patient. While family history and genetic testing are infrequently a source of disagreement when working to diagnose ACM,[45,46] ECG interpretation and MRI reads have been instead identified as the main culprit of diagnostic uncertainty for this disease.[45,47] In light of this, it is crucial to rely on expert cardiac imagers and cardiologists that are very familiar with this disease when evaluating diagnostic tests for ACM. Genetic testing should accompany this diagnostic evaluation as identification of a P/LP variant in an ACM-associated gene consistent with the phenotype significantly increases the likelihood an ACM diagnosis is accurate.[48] When diagnostic uncertainty exists, it is important to obtain a second opinion at a tertiary referral centre focused on diagnosis and management of ACM.[49] Hopefully, in the near future, additional tools aided by artificial intelligence will streamline the diagnostic process to patients benefit. While some preliminary experiences in this field exist,[50,51] their implementation is yet to be fully integrated within major healthcare systems.

Arrhythmic risk stratification

Once a diagnosis of ACM is reached, the next immediate step in management is individualized arrhythmic risk stratification of the patient aimed at defining a patient's risk of a cardiac arrest or fast ventricular tachycardia (VT), and determining the need for implantable cardioverter-defibrillator (ICD) implantation. The assessment of the absolute risk of VT/ventricular fibrillation of an individual patient is, however, not a trivial task and over the past 45 years a significant amount of research effort has been spent in a long quest for the identification of core risk factors for VAs in ACM.[52]

The strongest risk factor for the occurrence of future severe VAs is certainly represented by a prior episode of a sustained VA.[53,54] For those patients (often called 'secondary prevention' cases), the placement of an ICD is strongly recommended by all guidelines currently available.[1,2,55,56] For patients without prior sustained VA events, risk stratification is more complicated and a comprehensive work-up including an ECG, a 24-h Holter, and an MRI is required to start estimating that individual patient's risk. Although several risk factors including demographic features (i.e. younger age, male sex), ECG features (i.e. QRS fragmentation, presence of ≥3 leads with inverted T waves), Holter data (i.e. presence of non-sustained VT [NSVT], PVC burden) and imaging features (i.e. reduction in RV or LV ejection fraction [LVEF], presence of scarring at late gadolinium enhancement [LGE]) of patients with ACM have been clearly recognized in the past, their weighted integration into a single estimate of risk has only recently been achieved through the introduction of an ARVC Risk Calculator.[24] This calculator integrates seven key risk variables (age, sex, history of recent cardiac syncope, presence of NSVT, 24-h PVC burden, number of leads with inverted T waves, and RV ejection fraction) and provides a 5-year estimate of the risk of sustained VAs for a patient with those characteristics. In the past few years, the ARVC Risk Calculator has been widely adopted by the ACM community,[37,57,58] and it has been formally externally validated by two large independent studies, showing its good reliability across more than 1200 patients with ACM.[59,60] Additional studies have further shown that the arrhythmic risk associated with extensive sport participation in patients with ACM is captured by this tool.[57,61] Results of an invasive electrophysiological study can now be integrated into the risk calculator as well.[62] Although some caveats regarding its use remain (mostly associated with left-sided forms of ACM and some specific desmosomal genes—as detailed below), this tool has been shown to be superior to all other currently available risk stratification strategies for all-comer ACM patients who fulfil 2010 TFC and it has been endorsed as the main risk stratification strategy for patients with ACM and no prior VA event in the recent 2023 European Society of Cardiology cardiomyopathy guidelines.[1,63] Currently, no specific 5-year estimate of risk derived from the ARVC Risk Calculator is recommended as a threshold for a primary prevention ICD, with however the most robust data seems to indicate a potential threshold in the vicinity of the 15%–25% range of 5-year risk,[63,64] which accounts for the potential of a baseline overestimation of these tools.[65] It is however important to remember that a final ICD recommendation should happen within a shared-decision making framework with both the objective data and risk factors as well as the patient's individual set of values being incorporated in the final decision and not simply by a blind following of the output of a calculator, which is meant only to aid not replace individual physician expertise. Outside from the parameters included in the risk calculators and that are routinely obtained with simple, non-invasive clinical test, some additional prognostic information can be retrieved through invasive examinations, such as electro-anatomical mapping and endomyocardial biopsies.[37,42,44,66,67] The presence of large areas of low voltages or of fractionated late potentials, or the finding of an inflammatory component at endomyocardial biopsy have all been shown as negative prognostic markers for patients with ACM. However, no clear standardization of the role of these tests in risk stratification is available to date and these tests are most often performed as part of the diagnostic (endomyocardial biopsy) or therapeutic (electro-anatomical mapping during VT ablation procedures) component of ACM management.

Once a decision regarding the need for ICD implantation has been made, a longitudinal re-assessment of the arrhythmic risk is required during patient follow-up, as ACM is a progressive disease. For arrhythmic risk stratification purposes, ECG and Holter

Table 2 Comparisons of the currently available diagnostic criteria for arrhythmogenic cardiomyopathy

Criterion	1994 TFC13	2010 TFC[19]	2020 Padua[26]	
			Right-sided	Left-sided
Morphological				
Major	**By Echo:** • Severe dilatation and reduction of RV ejection fraction with no (or only mild) LV impairment • Localized RV aneurysms (akinetic or dyskinetic areas with diastolic bulging) • Severe segmental dilatation of the RV	**By Echo:** • Regional RV akinesia, dyskinesia, or aneurysm *and* 1 of the following: o PLAX RVOT ≥32 mm or PLAX/BSA ≥19 mm/m^2 o PSAX RVOT ≥36 mm or PSAX/BSA ≥21 mm/m^2 o *or* FAC ≤33% **By MRI:** • Regional RV akinesia or dyskinesia or dyssynchronous RV contraction *and* 1 of: o RVEDD to BSA ≥110 mL/m^2(male) or ≥100 mL/m^2 (female) o RVEF ≤40% **By RV angiography:** • Regional RV akinesia, dyskinesia, or aneurysm	**By Echo/MRI:** • Regional RV akinesia, dyskinesia, or bulging *plus* one of the following: • Global RV dilatation (increase of RVEDV according to specific nomograms) • Global RV systolic dysfunction (reduction of RVEF according to specific nomograms)	
Minor	**By Echo:** • Mild global RV dilatation and/or RVEF reduction with normal LV • Mild segmental dilatation of the RV • Regional RV hypokinesia	**By Echo:** • Regional RV akinesia or dyskinesia *and* 1 of the following (end diastole): o PLAX RVOT ≥29 to <32 mm or PLAX/BSA ≥16 to <19 mm/m^2 o PSAX RVOT ≥32 to <36 mm (corrected for body size [PSAX/BSA] ≥ 18 to <21 mm/m^2) o *or* fractional area change >33% to ≤40% **By MRI:** • Regional RV akinesia or dyskinesia or dyssynchronous RV contraction *and* 1 of: o Ratio of RVEDV to BSA ≥100 to <110 mL/m^2 (male) or ≥90 to <100 mL/m^2 (female) o *or* RVEF >40% to ≤45%	**By Echo/MRI:** • Regional RV akinesia, dyskinesia or aneurysm of RV free wall	**By Echo/MRI:** • Global LV systolic dysfunction (depression of LVEF or reduction of GLS), with or without LV dilatation (increase of LV EDV according to specific nomograms) • Regional LV hypokinesia or akinesia of LV free wall, septum, or both
Histology				
Major	**By EMB:** • Fibrofatty replacement of myocardium on EMB	**By EMB:** • Residual myocytes <60% by morphometric analysis (or <50% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on EMB	**By MRI:** • Transmural LGE (stria pattern) of ≥1 RV region(s) **By EMB** • Fibrous replacement of the myocardium in ≥1 sample, with or without fatty tissue	**By MRI:** • LV LGE ≥1 Bull's Eye segment of free wall (subepicardial or midmyocardial), and/or septum (excluding septal junctional LGE)
Minor		**By EMB:** • Residual myocytes 60%–75% by morphometric analysis (or 50%–65% if estimated), with fibrous		

Continued

Table 2 *Continued*

Criterion	1994 TFC13	2010 TFC[19]	2020 Padua[26]	
			Right-sided	Left-sided
		replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on EMB		
Depolarization *Major*	• Epsilon waves or QRS prolongation (>110 ms) in V_1–V_3	• Epsilon wave in the right precordial leads (V_1 to V_3)		
Minor	**By SAECG:** • Late potentials (SAECG)	**By SAECG:** • Late potentials in ≥1 of 3 parameters without a QRS ≥110 ms • Filtered QRS duration (fQRS) ≥ 114 ms Terminal QRS <40 μV and ≥ 38 ms • Root-mean-square voltage of terminal 40 ms ≤20 μV **By ECG:** • TAD of QRS ≥55 ms in V_1, V_2, or V_3, in the absence of complete RBBB	**By ECG:** • Epsilon wave in V_1 to V_3 • TAD of QRS ≥55 ms in V_1-V_3 in the absence of complete RBBB	**By ECG:** • Low QRS voltages (<0.5 mV peak to peak) in limb leads (in the absence of obesity, emphysema, or pericardial effusion)
Repolarization *Major*		• TWI in V_1, V_2, and V_3 or beyond in individuals >14 years of age in the absence of complete RBBB	• TWI in V_1,V_2, and V_3 or beyond in individuals with complete pubertal development in the absence of RBBB	
Minor	• Inverted T waves in V_2 and V_3 in people age >12 years, in absence of RBBB	• Inverted T waves in V_1 and V_2 in individuals >14 years of age in the absence of complete RBBB or in V_4, V_5, or V_6 • Inverted T waves in V1, V2, V3, and V4 in individuals >14 years of age with RBBB	• TWI in V_1 and V_2 in individuals with completed pubertal development in the absence of RBBB • TWI in V_1,V_2,V_3 and V_4 in individuals with completed pubertal development with RBBB.	• TWI in V_4-V_6 in the absence of complete LBBB
Arrhythmias *Major*		• NSVT or sustained VT of LBB morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL)	• Frequent ventricular extrasystoles (>500 per 24 h), NSVT or sustained VT of LBBB morphology	
Minor	• LBBB VT (sustained or non-sustained) • Frequent PVCs (>1000 per 24 h) at Holter	• NSVT or sustained VT of RVOT configuration, LBBB morphology with inferior axis (positive QRS in leads II, III, and aVF and negative in lead aVL) or of unknown axis • >500 PVCs per 24 h (Holter)	• Frequent PVC (>500 per 24 h), NSVT or sustained VT of LBBB morphology with inferior axis ('RVOT pattern')	• PVC (>500 per 24 h), NSVT or sustained VT with RBBB morphology (excluding 'fascicular pattern')
Family history/ Genetic *Major*	• Familial disease confirmed at necropsy or surgery	• ARVC confirmed in first degree relative meeting TFC	• ACM confirmed in first degree relative who meets diagnostic criteria • ACM confirmed pathologically in first degree relative	

Continued

Table 2 ***Continued***

Criterion	1994 TFC13	2010 TFC[19]	2020 Padua[26]	
			Right-sided	Left-sided
		• ARVC confirmed pathologically in first degree relative • Identification of P/LP mutation associated with ARVC	• Identification of a P/LP ACM mutation	
Minor		• Family history of SCD at <35 years due to suspected ARVC • Family history (clinical diagnosis based on present criteria)	• History of ARVC in first degree relative in whom it is not possible or practical to determine whether the family member meets current TFC • Premature SCD at <35 years of age due to suspected ARVC in first degree relative • ARVC confirmed pathologically or by current TFC in second degree relative	• History of ACM in first degree relative in whom it is not possible or practical to determine whether the family member meets diagnostic criteria • Premature SCD at <35 years of age due to suspected ACM in a first degree relative • ACM confirmed pathologically or by diagnostic criteria in a second degree relative

ACM, arrhythmogenic cardiomyopathy; EMB, endomyocardial biopsy; NSVT, non-sustained ventricular tachycardia; PLAX, parasternal long axis; PSAX, parasternal short axis; PVC, premature ventricular complexes; RVOT, right ventricular outflow tract; SCD, sudden cardiac death; TAD, terminal activation delay; TFC, task force criteria; TWI, T wave inversion.

should be repeated yearly, with structural assessments being repeated less frequently (1–3 years for echo; 2–4 years for MRI), as the morphological progression of disease is reported to be slower and to happen later than its electrical progression.[68,69] Changes in those tests (especially in the PVC burden on Holter) can be used to identify phases of active disease and updated values entered into the ARVC Risk Calculator to achieve longitudinal risk stratification.[70,71] Clinical longitudinal monitoring of a patient with these tests allows for the identification of the optimal time point for an ICD implantation if an ICD had not been implanted at initial presentation.

Shocks and arrhythmia management

The third pillar in the management of patients with ACM is reducing the risk of sustained VAs and ICD therapies. Management of VAs is generally achieved through a combination of lifestyle changes, medications, and catheter ablation procedures.

In general, patients with ACM should be counselled to limit endurance and competitive physical exercise, as endurance exercise has been shown to increase the arrhythmic risk of probands and family members alike,[72–75] and to cause progression of the structural component of disease.[76,77] Some gene-specific differences regarding the relative impact of exercise on disease progression, however, have been increasingly reported. Specifically, patients harbouring P/LP variants in the plakophilin-2 gene seem to be at the highest risk of detrimental effects from exercise while *PLN* variant carriers seem to be significantly less affected.[72,78] These data seem to suggest the need for a more nuanced approach in exercise restriction guidance, but further studies are needed prior to the generation of a gene-specific algorithm. Still, when exercise restrictions are recommended, although no clear optimal threshold of exercise exposure has been identified, current clinical consensus is to limit their exercise exposure to the amount recommended by the American Heart Association for cardiovascular risk reduction (150 min of moderate-intensity aerobic activity per week).[79] Just with this lifestyle change, a significant arrhythmic risk modulation has been observed both in probands with ACM and their gene-positive family members across several studies.[75,80] Nonetheless, even after implementing exercise restriction, patients with ACM remain at a much higher arrhythmic risk than the general population and a significant percentage of them remains symptomatic for palpitations and experience sustained VA or ICD therapies during follow-up.[81,82]

Pharmacological therapies represent an important additional step in the management of this patient population. Beta-blockers are the guideline-recommended first-line therapy for all patients with ACM, due to their reduction of the adrenergic tone and arrhythmic risk.[1,2] No significant data exist comparing specific beta-blockers or non-selective vs selective beta-blockers, but metoprolol and bisoprolol have been the most commonly reported beta-blockers across different studies.[83–85] Regardless of the beta-blocker employed, progressive up-titration of its dosage to the maximal tolerated amount is also often recommended, as a dose >50% of the maximal prescribable dose was found to be associated with a reduction in major VAs in a large cohort study.[83,86] Flecainide represents a safe, well tolerated and effective combination agent to add to the baseline beta-blocker therapy for the control of arrhythmias and arrhythmia-related symptoms in patients with ACM,[1] with recent observational studies reporting its safety even in patients without an ICD or with left-sided forms of disease.[87,88] Finally, amiodarone represents

the therapy of choice when other anti-arrhythmic medications fail to control the arrhythmic burden of disease and the patient has failed or is not a candidate for VT ablation. Amiodarone is a second-line drug due to its well-known side effects. In case of continuous arrhythmic breakthrough after lifestyle changes implementation and on optimized medical therapy, catheter ablation should be considered.[1,2] Although the overall risk of new arrhythmic events after catheter ablation remains high, numerous studies have reported significant reduction in the burden of VT and/or ICD shocks in patients with ACM, especially when an epicardial approach is pursued.[89–91]

VT ablation represents another potentially helpful therapeutic intervention for patients with ACM. It is generally offered to patients with VAs refractory to exercise restriction and medical therapy or with frequent ICD shocks. Considering the extended epicardial substrate that many patients with ACM have, a endo-epicardial approach is very often needed for effective treatment.[92,93] Compared with the relative poor outcomes observed in other non-ischaemic cardiomyopathies, in classical, RV-dominant ACM forms the overall success rate has been shown to be fairly good, resulting as high as 70% at 5 years (although often requiring re-do procedures).[91,94] VT ablation outcomes for LV-dominant or biventricular forms are instead less good, due to an often complex and fragmented substrate that may be difficult to target.[95–97] It is important to stress, however, that in neither case VT ablation has been proven an alternative to ICD implantation in patients at a high risk of VA.

Prevent heart failure and structural progression

Although VAs are the main manifestation of disease in patients with ACM, the increased overall survival, achieved thanks to earlier disease diagnosis and prevention of sudden death due to ICD implantation, has rendered the structural progression of disease and the associated heart failure (HF) episodes one of the modern problems of ACM management. The lifetime prevalence of signs and symptoms of HF in patients with ACM is reported to be as high as 50%,[98] with certain genotypes (i.e. *DSP* or *DSG2/DSC2*) more likely to develop HF signs and symptoms and potentially more prone to quicker HF development.[27,99,100] No specific guidance on HF therapy in patients with ACM is currently available and the current clinical recommendation is to adhere to the currently available general guidelines for HF management. Involving an HF specialist in the care of patients with ACM early in their disease course is often times helpful, especially when consideration for advanced therapies and appropriate timing for heart transplant are on the horizon.[101] Finally, the role of immune-modulatory medications as potential disease-modifying therapies has been proposed for some genetic-forms of ACM, to limit the overall inflammation associated with this disease and help with HF and structural prevention.[102–105] These data, however, are for now still experimental and should only been implemented with great caution, as well as with the support of colleagues significant expertise in the field of inflammatory cardiomyopathies.

Family screening

The final pillar of ACM management is family screening to facilitate early diagnosis, risk stratification, and management of relatives. ACM is typically characterized by autosomal dominant inheritance with age-related and reduced penetrance and considerable variability in outcomes even among members of the same family. Current guidelines recommend cardiac screening of first-degree relatives of ACM patients with an ECG, Holter monitor, and cardiac imaging beginning by age 10–12 with re-evaluations every 1–3 years.[1,2,56,106] The penetrance of ACM in the context of family screening is relatively high.[107] Studies show the yield of a baseline cardiac evaluation in at-risk relatives is approximately one in three with another one-third diagnosed during longitudinal evaluation.[108,109] The incidence of definite ARVC diagnosis in relatives peaks between in early adulthood with cases diagnosed prior to puberty rare.

Identification of a causative genetic variant in an ACM patient facilitates family screening to identify relatives carrying the identical variant that may lead to the associated phenotype. This is done through a systematic approach ('genetic cascade testing'), whereby genetic testing is initially offered to first-degree relatives (i.e. parents, siblings, and offspring) of an individual with a (likely) pathogenic variant. If a relative is found to carry the same variant, subsequent testing is extended to their first-degree relatives. This stepwise process continues through successive branches of the family, facilitating the early identification and surveillance of at-risk individuals while those that do not carry a definitively causative genetic variant can be discharged without clinical follow-up.

A longitudinal cardiovascular screening strategy for at-risk ACM relatives should recognize that structural progression is generally slow and that abnormalities on ECG and Holter monitoring usually precede detectable changes on imaging.[108–110] It is likely that longitudinal family screening can be improved by personalizing approaches by genotype, as well as by the age, baseline phenotype, and exercise plans of each relative. Broadly, studies suggest that relatives of ACM patients with no causative variant detected on comprehensive genetic testing have a lower risk of themselves developing ACM than relatives of gene positive patients, particularly when the proband in the family is an athlete.[77,111] Gene-specific approaches to family screening have also been proposed. A longitudinal screening algorithm for relatives with a P/LP *PKP2* variant was recently developed, showing how in most cases electrical criteria became apparent in gene-positive family member prior to any structural criteria being identified.[112] Such an approach has the potential to reduce screening burden while maintaining the benefits of diagnosis well before risks of VAs emerge highlighting. Among *PKP2* gene carriers, three main risk profiles of disease progression (requiring therefore the different screening intensities) were in fact identified: gene-positive family members with borderline disease at baseline (highest risk of disease progression; need yearly evaluation); gene-positive younger or symptomatic family members (intermediate risk of progression; partial re-evaluation every 2 years, complete re-evaluation over 4 years); gene-positive older and asymptomatic family members (low risk of progression, complete re-evaluation every 5 years). The hope is to have similar data available for all causative genes in order to maximize the yield of all screening tests for gene-positive members of patients with ACM.

Moving towards a gene-specific approach

While historically ACM genetic testing was recommended primarily to guide family screening and facilitate early diagnosis

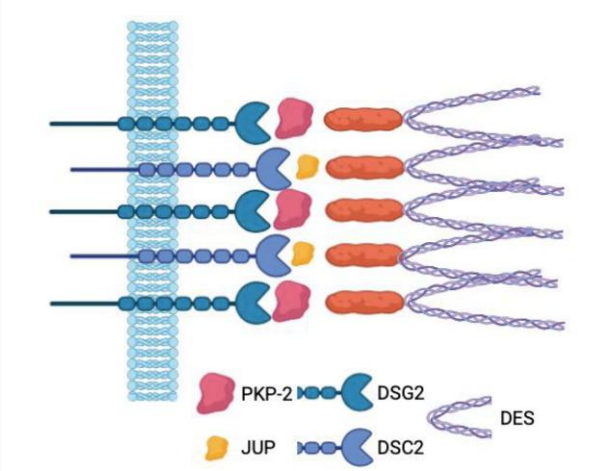

Figure 3 Schematic of the hemidesmosome

of at-risk individuals, today genetic testing is also recommended to inform diagnosis and management. In 50%–60% of individuals with ACM, an underlying monogenetic cause (i.e. P/LP variant) can be identified. For patients fulfilling 2010 TFC, causative variants are mainly in genes encoding proteins of the cardiac desmosome ('desmosomal genes'), an important structure that is part of the intercalated disk that provides cardiomyocyte cell–cell interaction. These genes include *PKP2*, *DSP*, *DSG2*, *DSC2*, and *JUP*, but also genes encoding proteins of structures closely related to the cardiac desmosome, including *DES* and *CDH2*[48] (*Figure 3*). Specific variants in *TMEM43* [p.(S358L)] and *PLN* [p.(R14del)] have also been associated with ACM.

Although the value of a gene first approach to diagnosis and management of ACM has become increasingly recognized across guidelines and scientific statements,[1,2,113] the importance of genotype in ACM has been clear for a long time. In the early 2000s, significant genotype–phenotype correlations were described by multiple groups, with the initial focus on gene-specific phenotypic spectra (i.e. providing descriptions of what phenotypes were associated with variants in a specific gene, for instance, causative desmoglein-2 [*DSG2*] or *PLN* variants).[114,115] Genotype was also recognized as one of the drivers of disease onset, progression, and outcomes in large cohort studies, with gene-positive patients showing earlier onset than gene-elusive patients.[116,117] In more recent times, Protonotarios *et al.* confirmed that the performance of arrhythmic risk stratification tools was significantly impacted by the underlying genotype.[59] Interestingly, several of the risk factors for patients with ACM are also common arrhythmic risk factors for other phenotypical forms of cardiomyopathies (such as dilated cardiomyopathy or non-dilated left ventricular cardiomyopathy) often arising from genes also associated with ACM (i.e. *DSP* or filamin C).[118–120] Building on these findings, Paldino and colleagues showed that although variants in several ACM-associated genes led to the development of various clinical phenotypes (ranging from dilated cardiomyopathy to ARVC to left-sided ACM), the arrhythmic event rates of patients with variants in the same genes appeared similar, regardless of the expressed phenotype.[121]

These studies supported a classification of patients based on their underlying genetic background rather than on the fulfilment of any set of phenotypic criteria and led to the creation of multiple gene-first clinical efforts by the ACM community. Similar efforts had in fact been attempted in the past (van der Zwaag *et al.*[115] Smith *et al.*[25]) to better characterize forms of ACM arising from specific genes or variants that present unique clinical characteristics or specific national clusters. The recent frequency and the breadth of gene-first efforts in ACM, however, has been unprecedented and has helped improve our understanding of many of the genetic forms of ACM. The genes with at least moderate levels of evidence for pathogenesis of ACM, with their clinical characteristics, are reported in *Table 1* and shortly recapped below.[48]

Plakophillin-2 cardiomyopathy

Variants in plakophillin-2 (*PKP2*) are the most common genetic variants associated with ACM.[16] Therefore, most of the gene-positive data present in the literature have been derived from patients harbouring P/LP variants in *PKP2*. Clinically, these patients present with the development of a classic, RV-dominant ACM phenotype (e.g. ARVC). They are at a high arrhythmic risk and they are particularly prone to the detrimental effects of physical exercise.[122,123] An arrhythmic presentation is often the first presentation of these patients, while HF episodes appear later in the natural history of disease, once the presence of overt disease (often at this point biventricular) is well established.[116,124]

Classical management strategies for ACM patients fit patients with a *PKP2* ACM well, as they represent the prototypical ACM patient. Of particular note, the translational data supporting the use of flecainide in patients with ACM is the strongest in *Pkp2* models, due to the interactions between the ryanodine-2 receptor (the direct target of flecainide), plakophilin 2, and cardiomyocyte intracellular calcium levels.[74,125] No gene-specific risk stratification tool currently exists for patients with ACM harbouring *PKP2* P/LP variants. Nonetheless, the current ARVC risk stratification has been shown to perform the best in patients with RV forms harbouring *PKP2* variants.[37,59] This is likely due to RV-dominant and *PKP2* positive forms representing the most commonly included forms in the derivation and validations cohorts supporting the ARVC risk stratification.[24,59,60]

Currently, P/LP *PKP2* variants represent the main target of several ongoing Phase I/II gene-therapy trials tailored for ACM patient. While safety and effectiveness data on these new viral-vector gene-therapies in ACM are currently limited to animal models,[126] there is hope that in the next decade or so radical advancements in the treatment of *PKP2* based ACM can be achieved.

Plakoglobin cardiomyopathy

Variants in the plakoglobin (*JUP*) gene were the first to be discovered associated with the development of ACM.[14] Originally, homozygous recessive variants were associated with the development the cardio-cutaneous 'Naxos syndrome', named for the area with the first description and highest prevalence of this condition. While these homozygous recessive forms represent the vast majority of *JUP*-associated ACM cases, a few cases of autosomal dominant *JUP*-based ACM have been reported as well.[127]

Most of the current evidence applying to *PKP2*-based ACM seems to apply to *JUP*-based ACM as well, with the clinical

phenotype of *JUP*-based ACM presenting most frequently as RV-dominant forms.[128] A cutaneous involvement (with woolly hair and palmo-plantar keratoderma) is observed in patients with recessive (homozygous/compound heterozygous) *JUP*-based ACM, generally developed in early infancy.[129] Although gene-specific evidence for *JUP*-based ACM is limited, a recently started multi-national collaboration (named NAXCARE) is aiming to shed additional light on this specific form of cardiomyopathy.[130] For clinical purposes, their management is overlapping with *PKP2* management.

Desmoplakin cardiomyopathy

P/LP variants in *DSP* have been associated with the development of very aggressive forms of left-sided ACM, often called *DSP* cardiomyopathy.[25,99] This form of ACM is generally characterized by a mild to borderline reduction in the LV function, extensive scarring/LGE presence in the infero-lateral sub-epicardial segments of the left ventricle, and the frequent occurrence of myocarditis episodes (reported in 15%–30% of all *DSP* patients across several cohorts).[25,95,99] Most of these ACM phenotypes will present with a biventricular form, while isolated RV involvement, although possible, result generally not common.[25] Interestingly, a higher prevalence of female patients have been reported in *DSP* cohorts, with some studies suggesting that females may be at a higher arrhythmic risk (in contrast to other genetic and gene-elusive forms of ACM, where males are instead at higher risk of adverse events).[28,99,131]

A significant clinical conundrum in patients with *DSP* cardiomyopathy is the phenotypic differentiation of this disorder from LV scar caused by a non-genetically determined previous myocarditis, prior to the availability of genetic testing results. The main red flags that should trigger a clinical suspicion for *DSP* cardiomyopathy (or a genetic cardiomyopathy in general) are the persistence of HF signs and symptoms, a dilative left ventricle with regional wall motion abnormalities and/or the presence of extensive transmural scar or of a ring-like LGE pattern.[104,132–134] Additionally, a personal history of repeated myocarditis flares in the absence of a clear autoimmune or rheumatological diagnosis is also highly suspicious for this disease.[135]

Although myocarditis episodes and 'hot phases' of diseases have been reported in patients with ACM and multiple different genes,[136,137] they are certainly the most common in patients with *DSP*-based ACM.[138,139] These myocarditis episodes appear to be associated with physical exercise exposure and represent a significant event in the natural history of this disease. In fact, patients with this form of cardiomyopathy have been shown to have their risk of VA, and HF hospitalization significantly increased after the occurrence of myocarditis flares.[99,140] For that reason, inflammation and myocarditis episodes are currently being investigated as a potential therapeutic target in this population.[102,103,141,142] Preliminary data have shown a significant clinical impact of immunosuppressive medications in the modulation of long-term outcomes of patients with *DSP* cardiomyopathy but further studies and randomized controlled trials are needed to fully understand the benefit associated with the use of these medications.[102]

As the current ARVC risk stratification algorithm does not perform well in patients harbouring P/LP *DSP* variants,[59,143] even when they fully fulfil risk calculator requirements, a gene-specific risk calculator (the DSP Risk Score) has been developed.[28] This tool estimates the 5-year risk of VAs in carriers of P/LP variants of *DSP* regardless of their phenotype and has been shown performing well in development cohort and a small validation cohort. A larger validation cohort is currently being assembled.

Phospholamban p.(R14del) cardiomyopathy

P/LP variants in *PLN* are associated with all different major cardiomyopathy subforms.[144] Only one single specific variant, *PLN* c.40_42delAGA; p.(R14del), however, is associated with ACM hence referred to as *PLN* p.(R14del) cardiomyopathy. In a large study of 868 individuals with *PLN* p.(R14del), 21% had DCM while 9.4% fulfilled ARVC TFC at last follow-up, highlighting its multifacetedness.[145] Overall, the disease penetrance is very high, with up to 70% of individuals carrying a PLN p.(R14del) variant developing some form of cardiac phenotype by the age of 70.[145]

Individuals affected with *PLN* cardiomyopathy present with a high percentage of appropriate ICD therapy (47%), cardiac transplantation (18%), and a high rate of SCD <50 years in relatives.[115] A large follow-up study in 295 carriers (125 symptomatic at initial evaluation) demonstrated that after a median follow-up of 42 months, 19% developed a first episode of malignant VA while 11% had an end-stage HF event, underscoring the malignant character of *PLN* p.(R14del) cardiomyopathy. LVEF <45% and sustained or NSVT were independent risk factors for malignant VAs.[22]

A variant-specific risk calculator was later refined in nearly 700 individuals (without prior malignant VA) and identified reduced LVEF, PVC count/24 h, amount of negative T waves, and presence of low-voltage ECG as significant predictors.[33] This first variant specific VA risk calculator model had sustained good performance up to 3-year follow-up.[146] Several variant specific predictors of HF episodes and/or need for transplantation and mechanical support (LVEF, low voltages, New York Heart Association Class > II at first evaluation) have been recently identified as well.[147]

Desmoglein-2/desmocollin-2 cardiomyopathy

P/LP variants in the desmoglein-2/desmocollin-2 (*DSG2*/*DSC2*) genes have been associated with the development of a classical form of RV-dominant ACM.[17,18,148,149] Although variants in these genes present very similarly and these two cadherin genes are often grouped together, affected ACM patients with causative *DSG2* variants are 10× more common than those with *DSC2* variants.

The clinical presentation of *DSG2/DSC2* cardiomyopathy has been described as similar to *PKP2* cardiomyopathy, with however a few differences. First, the frequency of LV involvement in some studies have been reported higher than the one observed in *PKP2* classical RV-dominant forms,[150] although this finding has not been replicated in larger cohort studies.[27] Still, to date, no evidence of pathogenicity of either gene for isolated or predominant LV forms exists. Regardless of LV involvement, however, the frequency of HF episodes (both as first presentation or during follow-up) has been significantly higher than in *PKP2* cardiomyopathy, especially for *DSG2* cardiomyopathy and for patients with

common East Asian founder variants.[27,150] Second, digenic, compound heterozygous, and homozygous disease is more common than in *PKP2* cardiomyopathy and is associated with a more severe phenotype.[151] To date, large cohorts reporting gene-specific data on *DSG2/DSC2* cardiomyopathy are fairly limited and no gene-specific risk tool exist. Current recommendations are similar to those for *PKP2* cardiomyopathy, with only family screening considerations varying slightly in light of the high frequency of compound heterozygous and homozygous variants.

Filamin C cardiomyopathy

Although representing one of the genes only recently associated with the development of ACM,[23] P/LP variants in filamin C (*FLNC*) have important clinical significance in the field of ACM as they have been shown to lead to a very aggressive form of left-sided or biventricular disease with outcomes fairly similar to patients with *DSP*-based ACM.[30]

Gene-specific data were recently gathered under the Filamin C Registry Consortium effort and gene-specific risk factors (age, history of syncope, male sex, presence of NSVT, and LVEF) were identified and merged into a gene-specific risk stratification tool for SCD and major VAs.[29] This risk stratification tool showed good performance in its development cohort (C statistic of 0.76 [95% confidence interval 0.67–0.86] at 12 months) and its validation is currently being pursued.[29]

Desmin cardiomyopathy

Variants in the desmin (*DES*) gene have been rarely associated with the development of LV-dominant or biventricular forms of ACM,[21,152,153] normally more aggressive in males than in females.[154] It generally presents with a borderline reduced LVEF and with significant amount of LV LGE at MRI. The most characteristic clinical features of these forms of ACM, however, is the common presence of atrioventricular conduction disorders, reported present in up to 40% of carriers and often representing one of the main presenting symptoms.[154,155] No gene specific risk stratification strategies or managing recommendation is available for this population and the clinical suggestion is to follow umbrella ACM clinical management guidelines, with the single exception being the type of ICD device offered that needs preferentially to be a transvenous ICD, considering the high rate of pacing requirement that these patients almost inevitably develop during follow-up.

TMEM43 cardiomyopathy

The *TMEM43* c.1073C > T, p.(S358L) variant is associated with a highly malignant form of biventricular- or LV-dominant form of ACM, most commonly observed in the Canadian regions of Newfoundland and Labrador.[20] *TMEM43* cardiomyopathy is characterized by an early onset risk of SCD, particularly in males, and a very high rate of HF.[20,156] ICDs (and very often cardiac resynchronization devices, given the frequent presence of HF with reduced ejection fraction and left bundle branch block) are commonly placed in patients with *TMEM43* cardiomyopathy, with sex-dependent considerations regarding timing of device implantation. Genotype positive males are at a particularly high risk of SCD, that can represent the first clinical manifestation of disease. For this reason, male carriers of *TMEM43* c.1073C > T variants are recommended the placement of an ICD prophylactically after 18 years of age and regardless of the presence of any phenotypic features.

Advantages and limitations of a gene-first approach in ACM

The novel gene-first approach to ACM has the potential for revolutionizing our understanding and treatment of this disease. The main advantage of such an approach is certainly the possibility of reaching a degree of granularity in disease characterization that a 'one-size fits all' phenotypic classifications could never achieve. The individual clinical characteristics associated with different genes are amplified in such an approach and genotype-positive patients without a fully developed phenotype can be more precisely assessed. Additionally, by proceeding in a gene-specific fashion, more uniform research can be performed, leading to more tailored patient care. Finally, with gene therapy technologies entering the field of cardiology and cardiovascular care, an ACM gene first classification and framework will greatly help in potentially implementing these new therapeutic experiences into clinical practice. For this reason, the recent 2024 Zurich ACM meeting gathered a large international panel to draft a new expert consensus on a gene-first approach to ACM. Publication is expected in 2026.

Nonetheless, some limitations of a gene-first approach are to be mentioned. First, in almost all probands, the first trigger of a clinical evaluation (which usually precedes genetic testing) is the presence of a phenotype or an arrhythmic event. One of the future questions that the ACM field will have to answer is certainly how to implement routine genetic testing without delaying care and in a cost-effective manner. Additionally, if genetics is the basis of classification and is to become the main driver of risk stratification and management, significant efforts to periodically re-evaluate variant classification, particularly for variants of unknown significance, must be implemented. It is also important to consider that in addition to the relevance of genetic testing for diagnosis, prognosis and therapy, a positive genetic test result can inform reproductive decision-making as it enables information on the pattern of inheritance, recurrence risk, and management of risk by prenatal or preimplantation diagnostics. Genetic testing in the context of familial disease also has important potential psychological impact and pre- and post-test genetic counselling to cover all aspects of the potential genetic character of disease including implications for family members is widely recommended.

Finally, it should not be forgotten that about 40% of all ACM patients remain gene-elusive, even when large panel next generation sequencing or exome/genome sequencing is employed. While their adverse event rates are lower than gene-positive ACM patients, they are still much higher than the general population.[116] These patients appear similar to classical *PKP2*-based ACM patients, but specific data on this topic are murky and often confounded by the presence a non-insignificant degree of ACM phenocopies. Further efforts toward the characterization of patients with gene-elusive ACM are desperately needed, to make sure that no patient is left behind.

Conclusions

ACM is an inherited cardiomyopathy characterized by fibrotic or fibrofatty involvement of either ventricle that is associated with

an increased arrhythmic risk and SCD, especially among young and athletic patients. Accurate diagnosis and risk stratification for VA is needed at the time of first diagnosis. Exercise reduction and cascade screening represent key components for management of this disease. As the field of ACM is rapidly shifting towards a more genotype-centred clinical framing, understanding of the unique features of genes associated with ACM development will be of paramount importance to better tailor therapeutic interventions for patients in the very near future.

Supplementary data

Supplementary data are not available at *European Heart Journal* online.

Declarations

Disclosure of Interest

Nothing to declare.

Data Availability

No data were generated or analysed for or in support of this paper.

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