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Sudden death related cardiomyopathies – Arrhythmogenic right ventricular cardiomyopathy, arrhythmogenic cardiomyopathy, and exercise-induced cardiomyopathy☆,☆☆

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ABSTRACT

Sudden cardiac death (SCD) is a devastating possible outcome of all cardiomyopathies. The risk of SCD is increased in patients with structural heart disease and continues to increase as ventricular dysfunction worsens. There is, however, a subset of cardiomyopathy, so-called "arrhythmogenic cardiomyopathy" (ACM), that carries an inherent propensity for arrhythmia in all stages of the disease, even preceding ventricular dysfunction. The aim of this review is to identify cardiomyopathies, other than ischemic and dilated cardiomyopathies, that are associated with ventricular arrhythmias (VAs) and SCD. We discuss prevalence, diagnosis, natural history and management of arrhythmogenic right ventricular dysplasia/cardiomyopathy, ACM, and exercise-induced cardiomyopathy, with emphasis on the morbidity and mortality of VAs associated with these cardiomyopathies and how they can be mitigated through lifestyle modification, medical management, and implantation of cardioverter defibrillators.

Contents

Abbreviations: ACM, Arryhthmogenic cardiomyopathy; ARVC, Arryhthmogenic right ventricular cardiomyopathy; ALVC, Arryhthmogenic left ventricular cardiomyopathy; AVB, Atrioventricular block; CMR, Cardiac magnetic resonance; DCM, Dilated cardiomyopathy; EC, Exercise-induced cardiomyopathy; EF, Ejection fraction; FAC, Fractional area change; FLNC, Filamin C; HF, Heart failure; HT, Heart transplantation; ICD, Implantable cardioverter defibrillator; LMNA, Lamin A; LV, Left ventricular or ventricle; LVEF, Left ventricular ejection fraction; NSVT, Non-sustained ventricular tachycardia; PVC, Premature ventricular contraction; RMB20, RNA binding motif protein; RV, Right ventricle or ventricular; SCD, Sudden cardiac death; TFC, Task Force Defined Criteria; TMEM43, Transmembrane protein 43; TTN, Abnormal titin; VA, Ventricular arrhythmia; VF, Ventricular fibrillation; VT, Ventricular tachycardia.

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Introduction

Sudden cardiac death (SCD) is a devastating event. The risk of sudden death is increased in patients with structural heart disease. A significant portion of SCD cases are the result of an underlying cardiomyopathy.[1–3] Individuals with cardiomyopathy of any etiology are at risk of SCD, particularly as the severity of the cardiomyopathy increases and the left ventricular (LV) ejection fraction (EF; LVEF) declines. The term "arrhythmogenic cardiomyopathy" (ACM) refers to the subset of cardiomyopathies that can cause cardiac arrhythmias in all stages of the disease, even preceding ventricular dysfunction. This review article focuses on arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVC), ACM, and exercise-induced cardiomyopathy (EC). We will also review the indications for implantable cardioverter defibrillator (ICD) implantation, which successfully prevent SCD in these conditions.[4,5]

Arrhythmogenic right ventricular cardiomyopathy

In 1982, Frank Marcus reported a case series of 24 patients with right ventricular (RV) dysplasia, highlighting the propensity for ventricular arrhythmias (VAs).[6] ARVC is uncommon in the general population, with prevalence ranging between 1 in 2500 and 5000. In regions of Italy and Greece the prevalence is at the higher end of this range.[7] Despite being relatively rare, it is a leading identifiable cause of SCD in young athletes.[2]

ARVC is an inherited cardiomyopathy with an autosomal dominant pattern of inheritance, incomplete penetrance, and variable expressivity.[8] A pathogenic mutation can be identified in approximately two-thirds of those diagnosed with the disease.[9] The mutations most commonly involve the desmosomal proteins, including plakophilin-2 (PKP2), desmoplakin (DSP), desmoglein-2 (DSG2), desmocollin-2 (DSC2), and plakoglobin (JUP).[9] Less commonly, mutations in nondesmosomal proteins, including alpha-T catenin (CTNNA3), cadherin-2 (CDH2), phospholamban (PLN), transmembrane protein 43 (TMEM43), sodium voltage-gated channel alpha subunit 1 (SCN5A), lamin A/C (LMNA), desmin (DES), filamin C (FLNC), and titin (TTN) have been reported.[10] The pathological hallmark of ARVC is myocyte loss with fibrofatty replacement of the myocardium. Formation of scar begins in epicardial portions of the RV and progresses to the endocardium.[11]

Diagnosis

In 1994, an international Task Force defined criteria (TFC) for diagnosis of ARVC, and these criteria were modified in 2010.[12] Diagnosis is based on major and minor criteria from six categories: RV structure and function, RV myocardial histology, aberrant repolarization, aberrant depolarization, arrhythmia history, and family history (Table 1). Diagnosis of ARVC requires fulfillment of two major, one major and two minor, or four minor criteria from separate categories. These criteria are an improvement on the prior 1994 criteria, sensitivity increasing from 57 to 71% ($p = 0.001$) and specificity increasing from 92 to 99% ($p = 0.016$).[13] However, they lack sensitivity in cases where disease predominantly effects the LV. From the limited data available on diagnosis of left-dominant disease, cardiac magnetic resonance imaging (CMR) has been shown to be effective.[14] When considering the diagnostic criteria for ARVC, it is important to recognize that there is no single "gold standard" diagnostic test. Rather, the diagnosis is based on the results of a comprehensive evaluation including: clinical history, family history, symptoms, ECG, signal-average ECG, Holter monitor, echocardiogram and/or CMR, electrophysiologic testing, genetic testing, and in very select cases endomyocardial biopsy.

Clinical presentation and natural history

ARVC generally presents in young adults, beyond the age of 12 years. The initial manifestations of the disease are highly variable including palpitations, syncope, and SCD. An important subset of patients with ARVC are diagnosed while asymptomatic as the result of cardiac tests for other indications or following cascade family screening after diagnosis of a family member. A report from the Johns Hopkins and Dutch Interuniversity ARVC Registries provides information about clinical characteristics and presenting symptoms of patients with ARVC. Of 439 index patients, over 99% presented in their mid-teenage years or later, and the majority (approximately 80%) presented before the age of 50 years. The average age of presentation was in the fourth decade (36 ± 14 years). At the time of diagnosis, 95% were symptomatic. Arrhythmia was the most common presenting symptom, 56% of patients experienced sustained VA, and an additional 11% experienced cardiac arrest at the time of presentation.[9] Other common signs and symptoms at the time of presentation are syncope, atrial fibrillation, palpitations, and heart failure (HF).[15,16] Previous data showed that symptomatic HF develops in a modest proportion of patients, approximately one in eight.[9,13] However, a more recent study with longer term follow-up reported development of signs or symptoms of HF in 49% of patients, primarily exertional dyspnea.[17] Possible explanations for this dramatic increase are: 1) that volume overload and canonical signs of left HF are less common in ARVC, causing HF to be under estimated in previous studies, 2) improvement in management of ARVC and prevention of SCD have resulted in patients living longer and experiencing worsening ventricular dysfunction as the disease progresses.

The RV is nearly universally affected, with a classic phenotype of disease distribution in the "Triangle of Dysplasia", originally including the RV inferior wall, RV outflow tract and RV apex. However, in recent years the triangle of dysplasia has been redefined, based on CMR data from 74 patients, to include the RV basal inferior wall, the RV anterior wall, and the posterolateral LV wall.[18] Involvement of the LV is seen commonly in advanced cases. Data from two autopsy case studies showed that the LV was involved in 32% and 76% of patients and is primarily the result of disease progression from RV to biventricular disease, as opposed to isolated LV disease.[19,20]

It is important to recognize that ARVC is a progressive disease. No one is born with ARVC; rather, it appears over time. The fact that it is virtually unheard of to diagnose ARVC prior to the age of 12 years, and that the median age of diagnosis is in the fourth decade strongly supports the progressive nature of this condition. Echocardiographic evidence of gradual disease progression was observed in 85 patients who were followed over a median of 6.4 years. There was significant interpatient variability in progressive structural dysfunction. RV fractional area change decreased from 39% (IQR, 33–44%) to 34% (IQR, 24–42%) ($p < 0.001$) with a median rate of functional decline of −3.3% per 5 years (IQR, −8.9-1.2%). LVEF decreased from 55% (IQR, 52–60%) to 54% (IQR, 49–57%) ($p = 0.001$), median rate of decline was −0.2% per 5 years (IQR, −6.5-1.7%). Progressive decline in RV function was associated with depolarization abnormalities by TFC on baseline

Table 1
2010 task force criteria for diagnosis of ARVC.

	Major criteria	Minor criteria
RV structure and function	**TEE**	**TEE**
	• RV akinesia, dyskinesia or aneurysm *AND 1 of the following*	• RV akinesia, dyskinesia or aneurysm *AND 1 of the following*
	- PLAX RVOT ≥32 mm - PSAX RVOT ≥36 mm - Fractional area change ≤33%	- PLAX RVOT ≥29 to <32 mm - PSAX RVOT ≥32 to <36 mm - Fractional area change >33 to ≤40%
	MRI	**MRI**
	• RV akinesia, dyskinesia or dyssynchronous contraction *AND 1 of the following*	• RV akinesia, dyskinesia or dyssynchronous contraction *AND 1 of the following*
	- RV EDV to BSA ratio ≥ 110 mL/m^2 (male), ≥100 mL/m^2 (female) - RV EF ≤40%	- RV EDV to BSA ratio ≥ 100 to <110 mL/m^2 (male), ≥90 to <100 mL/m^2 (female) - RV EF >40 to ≤45%
	RV Angiogram	
	• RV akinesia, dyskinesia or aneurysm	
RV myocardial histology	**Endomyocardial biopsy**	**Endomyocardial biopsy**
	• Residual myocytes <60%, and fibrous replacement of RV free wall myocardium ± fatty replacement of myocardium	• Residual myocytes 60–70%, and fibrous replacement of RV free wall myocardium ± fatty replacement of myocardium
Aberrant repolarization	**Electrocardiogram**	**Electrocardiogram**
	• TWI in V_1, V_2 & V_3 in pts. >14 years old	• TWI in V_1 & V_2 or V_4, V_5 or V_6 in pts. >14 years old • TWI in V_1, V_2, V_3 & V_4 in pts. >14 years old with complete RBBB
Aberrant depolarization	**Electrocardiogram** Epsilon wave in V_1, V_2 & V_3	**Signal-average Electrocardiogram**
		• Filtered QRS ≥114 ms *OR 1 of the following*
		• Terminal duration of QRS ≥55 ms • Terminal duration of QRS ≥38 ms (if <40 μV) • Root-mean-square voltage of terminal 40 ms of QRS <20 μV
Arrhythmia history	• NSVT or sustained VT with LBBB morphology and superior axis	• NSVT or sustained VT LBBB morphology and inferior axis • >500 PVCs in 24-h period
Family history	• 1st degree relative with confirmed ARVC by Task force criteria • 1st degree relative with pathologic confirmation of ARVC on autopsy • Known pathogenic mutation	• 1st degree relative with ARVC and undetermined Task force criteria • 2nd degree relative with confirmed ARVC by Task force criteria • 1st degree relative <35 years old with SCD

Major and minor criteria are indicated for the six domains of the 2010 Task Force Criteria for diagnosis of ARVC. Definite ARVC = 2 major or 1 major +2 minor or 4 minor criteria from different categories; Borderline ARVC = 1 major +1 minor or 3 minor criteria from different categories; Possible ARVC = 1 major or 2 minor criteria from different categories. BSA – body surface area; EDV – end-diastolic volume; NSVT – non-sustained ventricular tachycardia; PLAX – parasternal long axis; PSAX – parasternal short axis; PVC – Premature ventricular contractions; RBBB – Right bundle branch block; RVOT – RV outflow tract; TWI – T wave inversion; VT – Ventricular tachycardia. Modified from Marcus FI, McKenna WJ, Sherrill D, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the Task Force Criteria. *Eur Heart J.* 2010;31(7):806–814.

electrocardiography; all but 1 of the patients with significant RV structural progression (decrease in RV fractional area changed >10%) had depolarization abnormalities on baseline ECG.[21] Another study addressing the issue of disease progression describes the course of 18 patients who underwent heart transplantation (HT) for ARVC: 13 for advanced HF and 5 for refractory ventricular tachycardia (VT). Mean ages of initial presentation and HT were 24 ± 13 and 40 ± 14 years, respectively; HT occurred 17.6 ± 13.3 years after symptom onset in those who underwent HT for HF and 14.7 ± 15.9 years after onset in those with VT predominance. These data show the progression of ARVC and patient decline takes a course that is generally prolonged.[22]

Management

Our approach to management involves five steps: ensuring the correct diagnosis, SCD risk stratification, minimizing ICD therapies, preventing disease progression, and cascade screening of family members.

Correct diagnosis

The first step in management is to be certain the diagnosis is correct. It is important to be aware of the 2010 diagnostic criteria and common mimics of ARVC, particularly cardiac sarcoidosis (CS), which has significant overlap with ARVC in clinical presentation. Common presenting symptoms of both diseases are palpitations, dyspnea, chest discomfort, syncope, and VAs. Investigation of 57 patients from the Johns Hopkins ARVC registry, 42 ARVC probands with desmosomal mutations and 15 patients with definite ARVC by TFC who were later diagnosed with CS, revealed distinguishing features that may be helpful in differentiating these two diseases. Compared to patients with ARVC, those with CS presented at a later median age (23 [IQR, 18–29] vs. 45[40–47] years), were more likely to have HF symptoms (0% vs. 33% of patients), PR interval prolongation (0% vs. 53%), second or third degree atrioventricular node block (0% vs. 67%), nonspecific intraventricular conduction delay (0% vs. 27%), reduced LV function (LVEF 63%[55–65] vs. 57%[35–60]), interventricular septal scar on CMR (11% vs. 42%), or mediastinal lymphadenopathy (0% vs. 27%).[23]

SCD risk stratification

Once the diagnosis of ARVD is secure, the next item to be addressed is SCD risk stratification and whether an individual's risk of SCD is sufficient to warrant implantation of an ICD. SCD is a common first presentation and remains a lifelong risk for those with ARVC. Of the 439 index patients in the Hopkins/Dutch cohort, 48 (11%) presented with SCD.[9] The risk of SCD has been shown to at least double in those who participate in competitive athletics.[24] ARVC is also an important cause of SCD in the general population. Data from Australia and New Zealand report ARVC accounting for 5% of all cases of SCD.[1]

ICDs have been shown to be effective in termination of lethal VAs and improve mortality in patients with ARVC. A study of 132 patients with ICDs showed a 24% projected improvement in survival, based on actual patient survival compared to ventricular fibrillation (VF)/flutter-free survival.[25] Similarly, Bhonsale and colleagues reported 19% improvement in estimated survival.[26] The benefit of ICD was also seen in the Hopkins/Dutch cohort, which reported death from SCD in 11 of the 63 patients (17%) who did not undergo ICD implantation, while only 2 of the 335 patients (0.6%) with an ICD died of SCD.[9]

The current recommendations of the International Task Force stratify patients with ARVC into three risk groups (high, intermediate, low) as a basis for guiding decision making for ICD implantation. 1) High-risk patients are those with a history of VT or VF leading to cardiac arrest, the risk of life-threatening VA events in this group is >10% per year and ICD implantation is recommended (Class I). By means of extrapolation of data for other cardiomyopathies, patients with severe dysfunction of the RV (RV-Fractional area change/FAC ≤17%) and/or LV (LVEF ≤35%) should receive an ICD for primary prevention (Class I). 2) Intermediate-risk patients are identified by consensus-established risk factors. Patients with ≥1 "major" risk factor (syncope, non-sustained VT [NSVT], RV-FAC 17–24%, or LVEF 36–45%) are reasonable candidates for ICD (Class IIa). Those with "minor" risk factors (premature ventricular contractions or PVCs >1000/day, clinical heart failure, young age, male gender, complex genotype, proband status, inducible VT on EP study, T-wave inversion in V_4, V_5, or V_6, etc.) may benefit from ICD placement (Class IIb). 3) The low-risk group is composed of patients or family members without identifiable risk factors. As these patients have a rate of life-threatening VA events <1% per year, ICD is not recommended.[27] The 2017 VT guidelines similarly recommend ICD for patients with a history of resuscitated SCD, sustained VT, or significant RV or LV dysfunction (Class I). Primary prevention ICD is only recommended in these guidelines for patients with a history of cardiac syncope (Class IIa).[28]

A recent individualized risk prediction model has been presented to calculate predicted 5-year risk of VA ($P_{VA\ at\ 5\ years}$) in patients with ARVC and no prior history of VA. In this observational study, 528 patients with definite diagnosis of ARVC from 14 tertiary care centers in 6 countries were followed for 4.8 years. The primary outcome of sustained VA, SCD, aborted SCD, or appropriate ICD therapy was met by 146 (27.7%) patients. Age, sex, cardiac syncope, NSVT, PVCs within 24 h, number of leads with T-wave inversion on 12 lead ECG, RV dysfunction were identified as risk predictors and used to develop the following model:

$$P_{VA\ at\ 5}\ \text{years} = 1 - 0.801^{\exp(PI)}$$

PI = 0.488*sex – 0.022*age + 0.657*history of recent cardiac syncope + 0.811*history of NSVT + 0.170*ln(24 h PVC count) + 0.113*Sum of TWI in anterior and inferior leads – 0.025*RVEF.

Patients who developed VA were accurately identified with this model (C-index 0.77, 95% CI 0.73–0.81). Compared to the current Task Force algorithm, this model appropriately identified the same number (89.9%) of patients who eventually developed VA while reducing the total number of ICD implantations by 20.6% ($p < 0.001$).[29] This online calculator can be accessed at https://arvcrisk.com/. While this calculator has been shown to be an improvement on the prior means of risk stratification, the results should be interpreted in the clinical context of each individual patient.

Suppression of ventricular arrhythmias and minimization of ICD therapy

Once ICD implantation has been considered, the next step is to suppress VA, by means of beta-blockers, antiarrhythmic medications, and exercise limitation. The current data regarding the use of antiarrhythmic medications are controversial, but limited data suggest that amiodarone may be beneficial in decreasing VA.[15,30] Our experience is that beta-blockers and amiodarone can be beneficial in decreasing symptomatic ventricular ectopy and VA. Beta-blockers are recommended for patients with a history of VA (Class I) and are also reasonable for

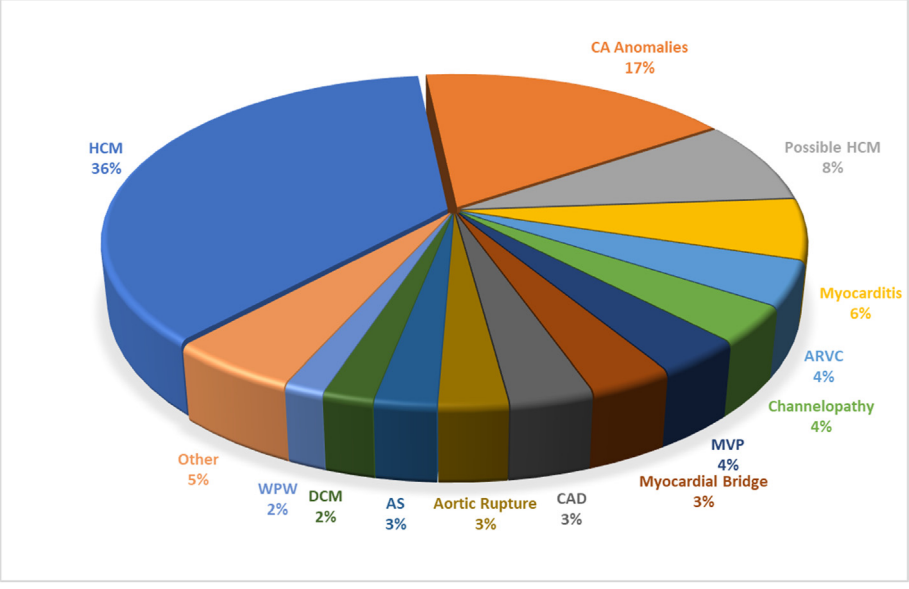


Fig. 1. Etiology of SCD Due to Cardiovascular Events. Cause of sudden death in 690 young competitive athletes who died as consequence of a cardiovascular event. ARVC – Arrhythmogenic right ventricular cardiomyopathy; AS – Aortic stenosis; CA – Coronary artery; CAD – Coronary artery disease; DCM – Dilated cardiomyopathy; HCM – Hypertrophic cardiomyopathy; MVP – Mitral valve prolapse; WPW – Wolff-Parkinson-White. Adapted from Maron BJ, Doerer JJ, Haas TS, et al. Sudden deaths in young competitive athletes: analysis of 1866 deaths in the United States, 1980–2006. Circulation. 2009;119(8):1085–1092.

those without history of VA (Class IIa).[27,28] Amiodarone is recommended for patients with frequent ICD discharges (Class I) and is reasonable for symptomatic patients with frequent PVCs and/or NSVT (Class IIa).[27] Flecainide may be a promising option for control of VA in patients with ARVC. Data from a small number of patients with recurrent VT showed complete resolution of VT with addition of flecainide to metoprolol or sotalol.[31]

Exercise participation is an important risk factor for SCD and ARVC-associated VT, which has been shown to be catecholamine-mediated.[32] ARVC accounts for 4–14% of SCD cases in young athletes in the United Kingdom and United States.[2,33–35] A prospective study from the Veneto, Italy region showed that 22% of SCD cases in young athletes were due to ARVC.[36] Fig. 1 shows the cause of SCD in the 690 cases confirmed to be of cardiac etiology. In 2003, another prospective cohort study analyzed all cases of SCD in young people in the Veneto Region of Italy over a 21-year period. Their results showed that individuals with ARVC were at increased risk of SCD with participation in sports (RR 5.4, CI 2.5–11.2; $p < 0.0001$). They also showed that SCD occurred earlier in individuals with ARVC who participated in sports, compared to those who did not (22 ± 4 vs. 27 ± 7 years; $p = 0.02$).[37] An observational study of 84 patients with ARVC who underwent ICD for primary prevention reported 63% were involved in exercise at the time of their first appropriate ICD discharge.[26] A study of exercise history in 37 desmosomal mutation carriers showed that development of the first episode of VA was associated with participation in high-intensity athletics in adolescence and higher lifetime exercise accumulation. Those who developed VA exercised significantly more (3.5-fold) than the American Heart Association (AHA)-recommended minimum, while those who exercised less than the AHA-recommended minimum did not experience VA ($p = 0.03$).[38] These data highlight the importance of exercise restriction in prevention of SCD and VA control. Participation in intense exercise is formally recommended against in patients with ARVC.[27,28,39] Exercise should not exceed the AHA-recommended minimum for healthy adults (12.5 Metabolic equivalent hours per week).[28,38] Further study is needed to more precisely define exercise thresholds for development of disease in mutation carriers and disease progression in those with symptomatic ARVC.

Catheter ablation is considered palliative therapy in patients with ARVC. Catheter ablation, particularly epicardial ablation, has been shown to significantly reduce VT burden. However, recurrence rates were considerable, ranging from 29 to 75%.[40–44] Catheter ablation is recommended (Class IIa) for those in whom beta-blockers provide ineffective symptomatic control.[27,28] However, it has not been shown to decrease the risk of SCD.[15]

Prevention of disease progression

As described above, ARVC is a progressive disease. The fourth aspect of management is to prevent, or delay, progression of the disease. Participation in sports and vigorous exercise increases the risk of development of clinically significant ARVC, earlier age of onset, progression of disease, HF, need for HT, VA, and SCD. The deleterious effects of exercise were described in a study of 87 patients from the Johns Hopkins ARVC registry. Athletes developed symptoms earlier (30 ± 13 vs. 41 ± 21 years) and were more likely to develop VA (34% vs. 0%, $p = 0.002$), HF (18% vs. 0%, $p = 0.012$), and meet TFC (82% vs. 35%, $p < 0.001$) than non-athletes.[45] Subsequent studies have supported these findings, showing increased likelihood of meeting TFC, developing symptoms, biventricular dysfunction, HT, VA and SCD in those who participate in athletics.[24,38,46] Given these findings, exercise limitation should be an important aspect of both prevention of disease in healthy gene carriers and controlling disease progression in symptomatic patients.

As beta-blockers reduce wall stress and may delay progression of myocardial damage in ARVC, they are recommended for all patients with right or left HF (Class I) and are reasonable for all patients, despite arrhythmia or HF status (Class IIa).[27] For patients with symptomatic right or left HF, angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, and diuretics are recommended, as per standard pharmacologic HF therapy.[27]

Cascade family screening

The final aspect of management is cascade family screening. Clinically significant disease manifests in approximately one-third of first-degree relatives of ARVC probands.[47] It is important to identify these individuals so appropriate lifestyle modifications can be made and disease manifestation/progression can be monitored. Screening for ARVC is recommended in first-degree relatives of probands (Class I).[28] In families of probands who carry a pathogenic mutation, first-degree relatives should undergo genetic screening. Family members in whom the same mutation is identified should have an initial cardiac evaluation at the time of mutation identification, then every 2–3 years. Cardiac evaluation should include 12 lead ECG, Holter monitor, and echocardiogram or CMR. These individuals should also be counselled on exercise restriction. In families of probands without an identifiable mutation, all first-degree family members should have a cardiac evaluation every 2–3 years. Fig. 2 shows that family members of probands with identifiable mutations have higher rates of ARVC-related symptoms, VA, and death than those of probands without identifiable mutations.[9]

Unanswered questions

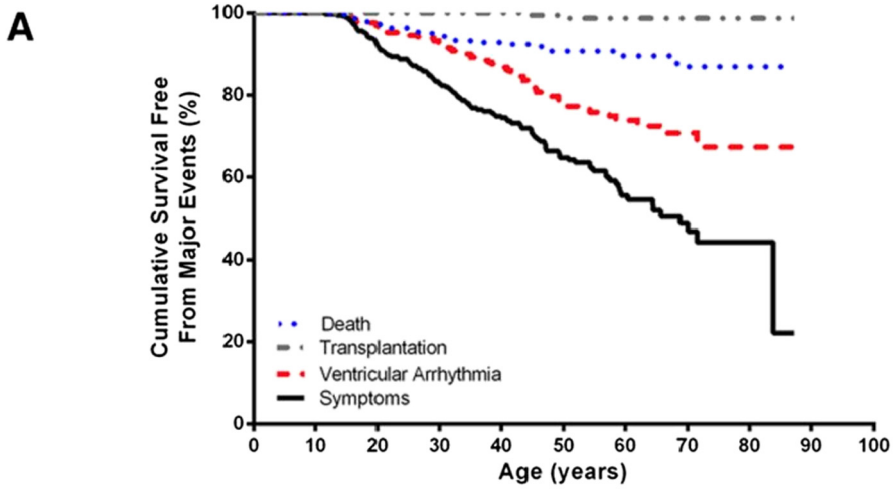
While tremendous progress has been made in understanding ARVC since the first paper by Marcus and colleagues, many questions remain unanswered. Some of the most pressing questions include: How can we improve the diagnostic criteria for ARVC, especially in left-dominant disease? What is the "safe level" of exercise for ARVC patients? Does a dramatic reduction in exercise once ARVC is diagnosed reduce the risk of SCD sufficiently to reduce the need for an ICD? What is the rate of progression of ARVC and how can it be reduced? How can we improve approaches to arrhythmia control in ARVC patients with drugs, ablation, and autonomic modulation? Can a medication be developed that will prevent development of ARVC?

Arrhythmogenic cardiomyopathy

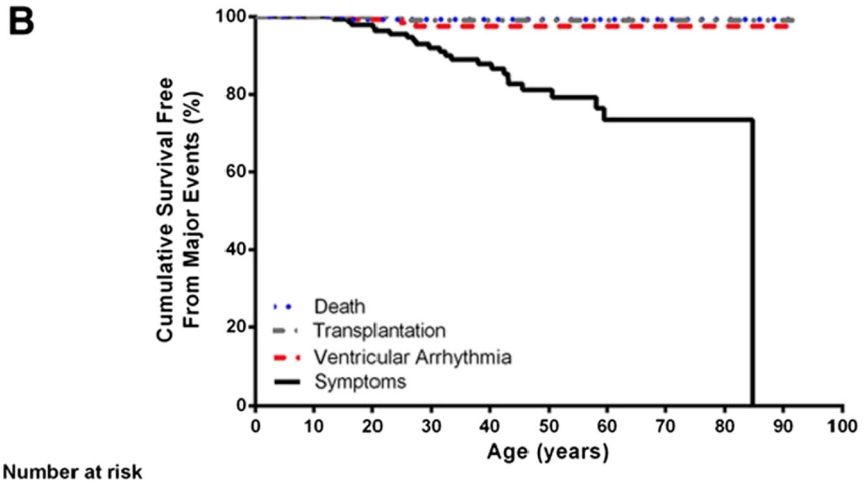
ACM is new classification of cardiomyopathy, initially proposed by Sen-Chowdhry and McKenna in 2010, that is yet to be precisely defined.[48,49] ACM is a disorder of the myocardium with predisposition for early VA and development of cardiomyopathy later in the disease course.[49] Genetic causes of ACM will be discussed in this section. Genetic disorders can be broken down into ARVC and arrhythmogenic left ventricular cardiomyopathy (ALVC). ARVC is most commonly associated with mutations in the desmosomal genes, whereas ALVC is associated with a broader spectrum of genetic abnormalities including mutations in genes encoding lamin A/C, filamin C, phospholamban, TMEM43, SCN5A, and RBM20.

ARVC is the most well-defined subset of ACM and has been discussed in detail in the previous section.

ALVC, also termed left-dominant arrhythmogenic cardiomyopathy, is a disease that originates in the myocardium of the LV, not to be confused with ARVC that has progressed to biventricular cardiomyopathy in later stages. ALVC was first reported in 1994 in 2 cases of SCD that revealed fibrofatty replacement of only LV myocardium.[50] An assessment in 2008 of 42 patients with ALVC provided valuable insight to identification of this disease.[51] VA with right bundle branch block morphology, T-wave inversions in the inferolateral leads, and relative preservation of RV function are points of distinction between ALVC and ARVC. Subepicardial and intramyocardial late gadolinium enhancement localized to the lateral and septal regions of the LV are characteristic findings on CMR. It is also notable that the authors of this article suggest that idiopathic myocardial fibrosis, which accounts for 6–16% of causes of SCD, may be a clinical manifestation of ACM, based on assessment of antemortem imaging and postmortem histology.[2,3,33,51]



Number at risk											
Death	385	372	318	258	205	134	70	27	6	0	0
Transplantation	385	372	318	258	205	132	69	27	5	0	0
Ventricular Arrhythmia	385	372	316	256	198	121	65	27	5	0	0
Symptoms	385	369	298	230	178	115	59	25	5	0	0



Number at risk											
Death	152	149	129	104	78	48	28	13	2	1	0
Transplantation	152	149	129	103	78	48	28	13	2	1	0
Ventricular Arrhythmia	152	149	129	102	78	48	28	13	2	1	0
Symptoms	152	149	128	98	74	44	25	13	2	0	0

Fig. 2. ARVC Complication-Free Survival. Freedom from ARVC-related symptoms, VA, SCD, and cardiac transplantation in family members of probands with pathogenic mutations (A) and family members of probands without identifiable mutations (B). Family members with mutations had more symptoms ($P = 0.004$), sustained VA ($P < 0.001$), and cardiac death (6 vs. 0 deaths) than family members without mutations. Cardiac transplantation-free survival was not to statistically different between the two groups ($P = 0.812$). Taken from 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. *Circ Cardiovasc Genet.* 2015;8(3):437–446, with permission.

Identification of a founder mutation (R14del) in the gene encoding phospholamban (PLN), originating in the Netherlands, was an important discovery in the classification of ACM.[52] Of 96 patients with ARVC and 257 with dilated cardiomyopathy (DCM), the R14del mutation was found in a significant proportion of patients with ARVC (12%) and DCM (15%). The patients with DCM and R14del mutation were found to have a higher risk phenotype than counterparts with DCM without R14del mutation, having more frequent ICD discharges (47 vs. 10%, $p < 0.001$) and HT (18 vs. 2%, $p < 0.001$).[52] These findings suggest that this subset of patients have a different natural history than those with DCM or ARVC, but no R14del mutation, and may be better categorized as ACM. Further, this could give a possible explanation for the significant clinical overlap between ARVC and DCM.

Symptoms in patients who carry the PLN R14del mutation develop at a mean age of 44–48 years.[52,53] The largest study of this cohort to date found that symptomatic individuals presented with VA (16%) or resuscitated SCD (4%), unexplained syncope (13%), or symptomatic HF (16%). Over a mean follow-up of 42 months, 19% had SCD or appropriate ICD therapy at a mean age of 47 years, 11% developed end-stage HF at a mean age of 53 years. Prognosis is poor for these patients, death being reported in early to mid-adulthood, with the highest mortality between ages 25 and 35 years.[53–55]

Lamin A and lamin C proteins are both encoded by the LMNA gene and are involved in structural support of the nucleus. LMNA mutations are a significant cause of familial cardiomyopathy and result in several distinct phenotypes.[56–58] Initial manifestations of cardiac disease include atrial fibrillation and abnormalities of the conduction system, which progress to VA and DCM, the two primary causes of morbidity and mortality.[57] In a study of 94 patients with LMNA gene mutations, 60 had phenotypic disease manifestations, all with cardiac involvement. Of these 60 patients, 77% had DCM with atrioventricular block (AVB) and 20% had DCM with VT/VF.[57] Analysis of a general DCM population showed that LMNA mutation was present in 33% of those with AVB.[58] Among patients with cardiac disease involvement, there is a high incidence (46%) of SCD.[59,60] A cohort of 269 LMNA mutation carriers revealed male sex, non-missense (insertion, deletion, or truncating) mutations, LVEF <45%, and NSVT as risk factors for development of VA.[61] Kumar and colleagues showed increased VA risk with accumulation of only 3 risk factors (male sex, LVEF <50%, non-missense mutation); over median follow up of 7 years VA occurred in 28% with 1 risk factor, 47% with 2 risk factors, and 69% with 3 risk factors.[62]

Filamin C serves an important role in anchoring sarcomeres to the plasma membrane of cardiomyocytes. Cardiomyopathy associated with mutations in the gene encoding filamin C (FLNC) have been implicated, but uncharacterized until recent years.[63] In 2016, Ortiz-Genga and colleagues identified 28 families affected by truncating FLNC mutations by screening 2877 individuals with inherited cardiomyopathy. From these families, 82 mutation carriers were identified: 28 probands and 54 relatives with mutation. Inheritance was in an autosomal dominant pattern and penetrance was high (>97%). VA, LV dilation, and myocardial fibrosis were common phenotypic characteristics. There was a high incidence of SCD, occurring in 40 (49%) individuals (12 probands, 28 relatives) from 21 of 28 families. Mean age of SCD was 44 ± 17 years.[64] Similarly, in 2018 Begay and colleagues reported VA or SCD in 11 of 13 patients identified with truncating FLNC mutations.[65]

Transmembrane protein 43 (TMEM43) is a nuclear envelope protein, with a founder mutation originating in Newfoundland, that has been identified in patients with ARVC and DCM. A study in 2013 of 285 patients affected by the TMEM43 mutation showed that important clinical characteristics were poor R wave progression and LV dilation. Symptom development (palpitations or presyncope) occurred at a median age of 40 years in males and was followed quickly by death at a median age of 45 years.[66] This rapid disease progression is particularly notable when compared to the slower progression of ARVC. Previous work has shown ICDs to improve mortality in these patients.[67]

Subunit alpha of voltage-gated sodium channel $Na_v1.5$ is encoded by the SCN5A gene and plays an important role in cardiac myocyte depolarization. Pathologic mutations in this gene were first reported in 1995 and were originally associated with electrical cardiac pathologies, such as long QT syndrome,[68] Brugada syndrome,[69] and Lenegre disease.[70] SCN5A-mediated ventricular dysfunction has been reported in small numbers of patients with DCM,[71] ARVC,[72] and LV noncompaction.[73] These patients have been shown to be at risk for both supraventricular and VAs.[73,74] Risk stratification of patients with SCN5A-mediated cardiomyopathy is not addressed in current guidelines, but consideration of ICD is recommended by Gacita and McNally in a recent publication (Fig. 3).[75]

RNA binding motif protein 20 (RBM20) participates in post-transcriptional modification of sarcomeric genes and has been implicated as a cause of hereditary cardiomyopathy since 2012 when it was found to be associated with abnormal titin (TTN) expression and DCM development.[76] Parikh et al. recently published findings from an RBM20 patient registry, consisting of 44 probands and 30 mutation positive family members. They identified locations of mutations in the RBM20 gene with the highest pathogenicity and provided a clinical description of RBM20 cardiomyopathy. Family history of SCD (51%) and cardiomyopathy (72%) was highly prevalent among probands. The age of diagnosis was 40 ± 12 years. In the complete registry, SCD occurred

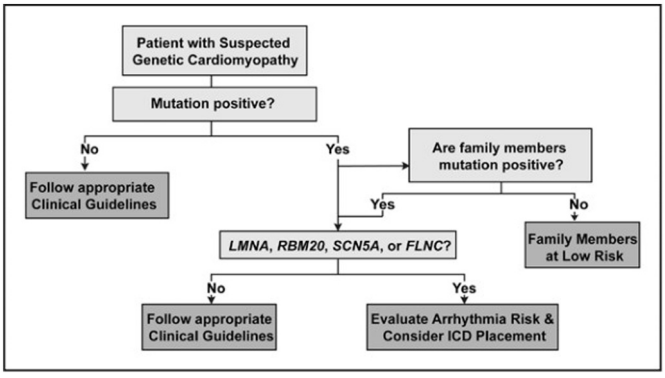


Fig. 3. Proposed Schema for Evaluation and Management of Patients with Arrhythmogenic Cardiomyopathy. Taken from Gacita AM, McNally EM. Genetic Spectrum of Arrhythmogenic Cardiomyopathy. Circ Heart Fail. 2019;12(3):e005850, with permission.

in 8% of individuals and appropriate ICD discharge in an additional 28% of individuals. NSVT (36%) and atrial fibrillation (17%) were also common. Among a subset of 30 individuals in the cohort with mutations in likely pathogenic regions, family history of SCD (93% vs. 51%, $p = 0.002$) and personal history of arrhythmia (66% vs. 43%, $p = 0.04$) were significantly higher compared to the rest of the cohort. When the probands ($n = 44$) from the cohort were compared to a large database of individuals with DCM ($n = 633$) and a cohort of those with TTN cardiomyopathy ($n = 83$), sustained VT (RBM20 = 20%; DCM = 2.2%, $p < 0.0001$; TTN = 1.2%, $p < 0.0001$) and NSVT (RBM20 = 36.0%; DCM 10.6%, $p < 0.0001$; TTN = 19.3%, $p = 0.03$) were more common in the RBM20 group. Finally, the RBM20 probands were compared to a LMNA cohort ($n = 122$), and the authors found no significant difference in VT or NSVT.[77] These data show that RBM20 cardiomyopathy has a high risk of arrhythmia that is more similar to LMNA cardiomyopathy than TTN or all-comers with DCM; therefore, SCD risk stratification and ICD implantation should be carefully considered for these individuals (Fig. 3). Longitudinal data from this RBM20 registry will be valuable in developing a systematic method of SCD risk stratification.

Clinical evaluation, diagnosis, and management

Currently, diagnostic criteria exist only for ARVC, and therefore careful evaluation is required for diagnosis of ACM in patients who do not meet criteria for ARVC. Given the considerable overlap of genetic mutations associated with ARVC, ALVC, and DCM, care should be taken to ensure the correct diagnosis. Establishing diagnostic criteria for ALVC will be important for further study of this disease and its natural history.

As in other cardiomyopathies, thorough patient and family history are valuable in differentiating diseases. Identification of family members with history of cardiomyopathy, SCD, or unexplained premature death, as well as events and symptoms preceding arrhythmic events, are important points of evaluation.

12 lead ECG and ambulatory ECG monitoring are necessary for diagnosis and establishment of VA or ventricular ectopy of predominant LV origin. Other diagnosis-suggestive changes such as PR prolongation or AVB (LMNA mutation), delayed depolarization or repolarization abnormalities (ARVC), T-wave inversions (ARVC or ALVC), low voltage or loss of precordial R waves (PLN R14del mutation) are less clearly defined but are important to note and follow over time.

Cardiac imaging with echocardiography or CMR is useful for identifying structural abnormalities. CMR is effective in identification of myocardial fibrosis and may be useful in the future for risk stratification of patients with ACM, but its role is yet to be clearly defined.[51,55,78,79]

The role of genetic testing is evolving. The current viewpoint is that genetic testing should be a supplement to clinical diagnosis and only genes recognized to be associated with specific diseases should be tested in individuals who meet clinical diagnosis for that disease.[80] In

the case of ACM, identification of high-risk mutations (i.e. LMNA, PLN R14del, TMEM43, RBM20) can guide further decisions on ICD implantation for prevention of SCD.

Medical management of ACM consists of management of arrhythmias and HF. Further research is needed for ACM-specific data on both aspects of management, so extrapolation from data specific to other cardiomyopathies should be considered at this time. Symptomatic arrhythmias, palpitations and inappropriate ICD therapy may be controlled by use of beta-blockers and antiarrhythmics, such as amiodarone and sotalol. Otherwise, guideline-directed medical therapy is recommended as described in the HF guidelines.[81]

In ACM, both left and RV dysfunction have been shown to increase proportionally with increased exercise.[46] Limited data suggest that exercise may increase risk of arrhythmias for patients with PLN and FLNC mutations. In patients with PLN mutations who developed malignant VA, 74% of the VAs occurred during exercise.[53] A smaller, but not insignificant, portion of patients with FLNC mutations developed sustained VA while exercising.[64] As with ARVC, it may be reasonable to also restrict exercise in these patients.

Risk stratification

Recommendation for risk stratification of ACM is incomplete in current literature and guidelines. Most of the data regarding risk factors for SCD come from ARVC and have been discussed in the respective section of this article. For patients with ALVC, ICD is recommended as secondary prevention for those who have experienced sustained VA or resuscitated SCD (Class I).[28] Those with LVEF <35% and symptomatic HF (NYHA Class II-III) should receive an ICD for primary prevention (Class I).[28,81] ICD is also reasonable for primary prevention in patients with a LMNA mutation and ≥ 2 risk factors: male sex, nonmissense (insertion, deletion, or truncating) mutations, LVEF <45%, and NSVT (Class IIa).[28,61] Given the high incidence of VA in patients with FLNC mutations, ICD is recommended by Ortiz-Genga et al., but not yet formally recommended in guidelines.[64] The recent elucidation of high propensity for arrhythmia in patients with RBM20 cardiomyopathy beckons careful monitoring for arrhythmias and evaluation for ICD until further data are available to guide risk stratification of these patients. Risk stratification of ALVC due to other mutations is not yet formally defined.

Exercise-induced cardiomyopathy

As discussed in the ARVC section, exercise participation is not only associated with increased arrhythmic events and disease progression, but also with diagnosis of ARVC in individuals that did not previously have disease or identifiable mutations associated with disease.[24,45] While it is established that exercise unmasks and exacerbates ARVC, extreme exercise may itself lead to development of EC, a pathologic condition that parallels ARVC, and yet is a distinct entity. Establishment of EC as an independent classification of cardiomyopathy is an emerging concept that requires further validation, the available data are summarized in this section.

Exercise has been shown to have greater effect on the RV than the LV, causing wall stress on the RV many times greater than that of the LV, resulting in RV remodeling over time.[82,83] RV dilation, RV dysfunction, and elevation in cardiac biomarkers have been shown to occur acutely in endurance athletes after prolonged exercise.[84,85] These acute and chronic, stress-induced changes to the RV myocardium may result in the formation of an arrhythmogenic substrate.

In 2003, Heidbuchel and colleagues reported findings from 46 endurance athletes, the majority being cyclists. All were high-level athletes, participating in exercise for at least 2 h a day, 3 times a week, for 5 or more years. Most of these individuals sought medical care for evaluation of palpitations, syncope or presyncope. Only 1 individual had a family history of VA. On initial evaluation, 37% had sustained VT, 52% had NSVT, and the remaining 11% had PVCs. The majority (80%) of ventricular ectopy had LBBB morphology, indicative of RV origin of arrhythmia. CMR was performed on 28 individuals, only 2 of whom showed infiltration of fat in the RV wall. When 2010 TFC for diagnosis of ARVC were applied to this population, 59% met criteria for definite ARVC and an additional 30% met criteria for probable ARVC. ICDs were implanted in 9 individuals. These 46 athletes were followed for a median of 4.7 years and 18 (39%) had arrhythmic events, 9 had SCD, 6 received appropriate ICD shocks, and 3 experienced sustained VT.[86] These data show evidence of development of arrhythmogenic disease in highly trained athletes, meeting criteria for ARVC in nearly 89% of individuals, despite the absence of the most typical hallmarks of ARVC, fibrofatty infiltration of the RV and familial disease, in all but a few individuals.

Subsequent work by these investigators in 2010 added genetic evidence to support the hypothesis of "exercise-induced right ventricular cardiomyopathy". Forty-seven athletes, whose mean exercise participation was 14 ± 9 h weekly for 19 ± 9 years, were studied. TFC for diagnosis of ARVC was met by 87% (51% definite, 36% probable). Yet, genetic testing of these individuals showed pathogenic desmosomal mutations in only 6 (12.8%) individuals, far below the previously published rate of mutation identification of 40% in patients with ARVC.[87] Members of the cohort without mutation exercised more than those with mutations (14.3 ± 8.9 vs. 9.2 ± 2.3 h per week, $p = 0.005$); no members of the cohort who exercised more than the mean (14 h per week) carried a mutation, but all met probable or definite clinical criteria for ARVC.[88] It is proposed that stress on the myocardium brought on by excessive amounts of exercise may compromise intracellular attachments without desmosomal mutations.

Sawant et al. added to these findings in 2014 by comparing the effects of exercise in 82 ARVC probands, 39 with desmosomal mutations and 43 without. This report supports previous findings that patients without desmosomal mutations exercised significantly more than those with mutations. Patients who participated in the top quartile of exercise intensity had significantly more structural disease and lower VT/VF-free survival.[89]

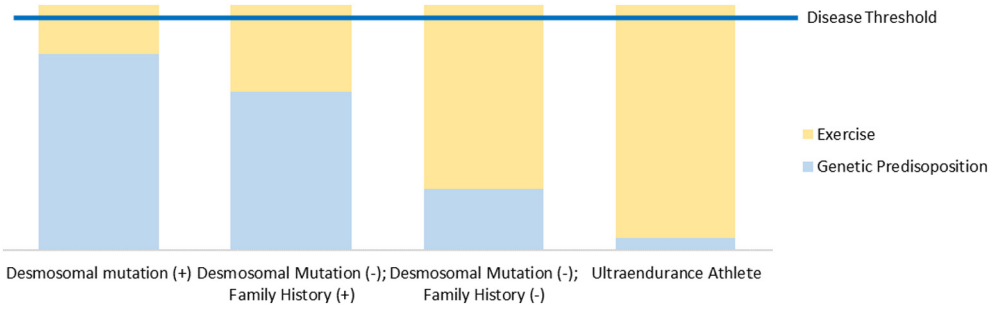


Fig. 4. Contribution of Genetics and Exercise to Development of EC. Representation of the proposed contribution of both genetic predisposition and quantity of exercise to meet a threshold for development of clinically significant RV cardiomyopathy. The far-left column represents desmosomal ARVC and the far-right column represents exercise-induced cardiomyopathy. Modified from 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. J Am Heart Assoc. 2014;3(6):e001471.

There are two ways to interpret these observations. The first is that EC is a distinct entity from conventional ARVC. The second perspective is that these patients represent a mutation-negative and family history-negative subset of ARVC. Analysis of our data, based on the Johns Hopkins ARVC registry, has found that the clinical course of patients with EC have a similar clinical course to patients with inherited ARVC.[89] What remains unclear is why some individuals develop EC and others do not. We suspect that there is an unknown factor that predisposes them to development of this cardiomyopathy. Fig. 4 illustrates the proposed concept of desmosomal ARVC and EC representing extremes of a spectrum of genetic predisposition and exercise contribution to development of a phenotypically similar disease. While the number of patients who participate in elite levels of exercise is high, it is most unusual to develop a cardiomyopathy. What differs between elite athletes who do and do not develop a cardiomyopathy remains to be determined.

Conclusions

ARVC is a well-established inherited cardiomyopathy. Although relatively rare, it accounts for a considerable portion of SCD. Given the propensity for arrhythmia and SCD, risk stratification is paramount. A novel risk calculator has been shown to be superior to the use of task force identified risk factors, however this should be externally validated. ACM and EC are new classifications of cardiomyopathy that have been presented in recent years. Further investigation is necessary to establish formal diagnostic criteria and a risk stratification model for ACM and validate the concept of EC.

Statement of conflict of interest

None of the authors have any conflicts of interests with regard to this publication.

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