

# 2019 HRS expert consensus statement on evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy



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## Abstract

Arrhythmogenic cardiomyopathy (ACM) is an arrhythmogenic disorder of the myocardium not secondary to ischemic, hypertensive, or valvular heart disease. ACM incorporates a broad spectrum of genetic, systemic, infectious, and inflammatory disorders. This designation includes, but is not limited to, arrhythmogenic right/left ventricular cardiomyopathy, cardiac amyloidosis, sarcoidosis, Chagas disease, and left ventricular noncompaction. The ACM phenotype overlaps with other cardiomyopathies, particularly dilated cardiomyopathy with arrhythmia presentation that may be associated with ventricular dilatation and/or impaired systolic function. This expert consensus statement provides the clinician with guidance on evaluation and management of ACM and includes clinically relevant information on genetics and disease mechanisms. PICO questions were utilized to evaluate contemporary evidence and provide clinical guidance related to exercise in arrhythmogenic right ventricular cardiomyopathy. Recommendations were developed and approved by an expert writing group, after a systematic literature search with evidence tables, and discussion of their own clinical experience, to present the current knowledge in the field. Each recommendation is presented using the Class of Recommendation and Level of Evidence system formulated by the American College of Cardiology and the American Heart Association and is accompanied by references and explanatory text to provide essential context. The ongoing recognition of the genetic basis of ACM provides the opportunity to examine the diverse triggers and potential common pathway for the development of disease and arrhythmia.

**KEYWORDS** Arrhythmogenic cardiomyopathy; Arrhythmogenic left ventricular cardiomyopathy; Arrhythmogenic right ventricular cardiomyopathy; Cascade family screening; Catheter ablation; Diagnosis of arrhythmogenic cardiomyopathy; Disease mechanisms; Electrophysiology; Exercise restriction; Genetic testing; Genetic variants; ICD decisions; Left ventricular noncompaction; Risk stratification; Treatment of arrhythmogenic cardiomyopathy.

**ABBREVIATIONS** ACE = angiotensin-converting enzyme; ACM = arrhythmogenic cardiomyopathy; AJ = adherens junction; AL = amyloid light-chain; ALVC = arrhythmogenic left ventricular

cardiomyopathy; AP = action potential; ARB = angiotensin receptor blocker; ARVC = arrhythmogenic right ventricular cardiomyopathy; AV = atrioventricular; BrS = Brugada syndrome; CMR = cardiac magnetic resonance imaging; COR = Class of Recommendation; CPVT = catecholaminergic polymorphic ventricular tachycardia; CRBBB = complete right bundle branch block; CT = computed tomography; DCM = dilated cardiomyopathy; ECG = electrocardiogram; EPS = electrophysiology study; FAO = fatty-acid oxidation; GJ = gap junction; HCM = hypertrophic cardiomyopathy; HF = heart failure; HFmrEF = heart failure with mid-range ejection fraction; HFrfEF = heart failure with reduced ejection fraction; HR = hazard ratio; ICCD = isolated cardiac conduction disease; ICD = implantable cardioverter defibrillator; ID = intercalated disc; IF = intermediate filament; JUP = junction plakoglobin; KSS = Kearns-Sayre syndrome; LBBB = left bundle branch block; LDB3 = LIM domain binding 3; LGE = late gadolinium enhancement; LM = lateral membrane; LOE = Level of Evidence; LQT1 = long QT syndrome type 1; LQT3 = long QT syndrome type 3; LQTS = long QT syndrome; LTCC = L-type calcium channel; LV = left ventricle; LVEF = left ventricular ejection fraction; LVNC = left ventricular noncompaction; MELAS = mitochondrial encephalopathy, lactic acidosis, and stroke; MERRF = myoclonic epilepsy with ragged red fibers; MET = metabolic equivalent; MLP = muscle LIM protein; MRI = magnetic resonance imaging; NCX = Na<sup>+</sup>/Ca<sup>2+</sup> exchanger; NGS = next-generation sequencing; NSVT = nonsustained ventricular tachycardia; NYHA = New York Heart Association; PFHB1 = progressive familial heart block type I; PVC = premature ventricular contraction; RBBB = right bundle branch block; RCM = restrictive cardiomyopathy; RV = right ventricle; RVEF = right ventricular ejection fraction; RVOT = right ventricular outflow tract; SCD = sudden cardiac death; SCN5A = sodium voltage-gated channel alpha subunit 5; SQTS = short QT syndrome; SR = sarcoplasmic reticulum; TAD = terminal activation duration; TRPM4 = transient receptor potential melastatin 4; TWI = T wave inversion; VF = ventricular fibrillation; VFL = ventricular flutter; VT = ventricular tachycardia; VUS = variant of uncertain significance; WES = whole exome sequencing; WGS = whole genome sequencing; ZASP = Z-band alternatively spliced PDZ-motif (Heart Rhythm 2019;16:e301–e372)

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## Section 1 Introduction

This international consensus statement is intended to help cardiologists and other health care professionals involved in the care of adult and pediatric patients with arrhythmogenic cardiomyopathy (ACM), which encompasses a broad range of disorders, by providing recommendations for evaluation and management and supporting shared decision making between health care providers and patients in a document format that is also useful at the point of care.

This consensus statement was written by experts in the field chosen by the Heart Rhythm Society (HRS) and collaborating organizations. Twelve societies collaborated with the HRS in this effort: the American College of Cardiology (ACC), the American Heart Association (AHA), the Asia Pacific Heart Rhythm Society (APHRS), the American Society of Echocardiography (ASE), the European Heart Rhythm Association (EHRA), the Heart Failure Society of America (HFSA), the International Society for Heart & Lung Transplantation (ISHLT), the Japanese Heart Rhythm Society (JHRS), the Latin American Heart Rhythm Society (LAHRS), the National Society of Genetic Counselors (NSGC), the Pediatric & Congenital Electrophysiology Society (PACES), and the Sociedade Brasileira de Arritmias Cardíacas (SOBRAC).

In accordance with the policies of the HRS, disclosure of any relationships with industry and other entities was required from the writing committee members ([Appendix 1](#)) and from all peer reviewers ([Appendix 2](#)). Of the 30 committee members, 16 (53%) had no relevant relationships with industry, including the document Chair and Vice-Chair. Sections that contain recommendations were written by committee members who were free of any relevant relationships with industry.

The writing committee reviewed evidence gathered by electronic literature searches (MEDLINE/PubMed, Embase, Cochrane Library). No specific year was chosen for the oldest literature. Search terms included but were not limited to the following: arrhythmogenic right ventricular cardiomyopathy, arrhythmogenic cardiomyopathy, dilated cardiomyopathy, lamin, ventricular tachycardia, ventricular arrhythmia, Fabry, noncompaction, phospholamban, cardiac amyloidosis, amyloid heart, heart failure, right ventricular failure, ARVC therapy, ARVC amiodarone, ARVC sotalol, ARVC flecainide, ablation, family screening, family risk, family member, relative, and electrocardiography. Evidence tables were constructed to describe the evidence, including study type, with observational cohorts representing the predominant form of evidence. Case reports were not used to support recommendations. This document also used a PICO

question to focus the search for evidence in [Section 3.12](#). A member of the writing committee, free of relationships with industry and educated in evidence-based medicine and clinical practice document methodology, oversaw the evaluation of the evidence and determination of the Level of Evidence (LOE) for each recommendation.

Recommendations were formulated using the Class of Recommendation (COR) and LOE system formulated by the ACC and AHA ([Figure 1](#)). This system provides a transparent mechanism to judge benefit relative to risk using a classification scheme (I, IIa, IIb, and III), supported by evidence quality and quantity using an LOE rating (A, B-R, B-NR, C-LD, C-EO); all recommendations are listed with a COR and LOE rating. For clarity and usefulness, each recommendation contains the specific references from the literature used to justify the LOE rating, which are also summarized in the evidence tables ([Appendix 3](#)). Recommendations based solely on the writing committee opinion are given an LOE rating of C-EO. Each recommendation is accompanied by explanatory text or knowledge “byte.” Flow diagrams and appropriate tables provide a summary of the recommendations, intended to assist health care providers at the point of care. A comprehensive discussion ([Section 4](#)) is presented to further the understanding of molecular mechanisms underlying ventricular dysfunction and arrhythmogenesis in ACM. For additional information on HRS clinical practice document development, please refer to the HRS methodology manual.<sup>1</sup> Clinical practice documents that are relevant to this document are listed in [Table 1](#).

To reach consensus, the writing committee members participated in surveys, requiring a predefined threshold of 75% approval for each recommendation, with a quorum of two-thirds of the writing committee. An initial failure to reach consensus was resolved by subsequent discussions, revisions as needed, and re-voting. The mean consensus over all recommendations was 94%.

An industry forum was conducted to achieve a structured dialogue to address technical questions and gain a better understanding of future directions and challenges. Because of the potential for actual or perceived bias, HRS imposes strict parameters for information sharing to ensure that industry participates only in an advisory capacity and has no role in either the writing or review of the document. This consensus statement underwent internal review by the HRS Scientific and Clinical Documents Committee and was approved by the writing committee. Public comment on recommendations was obtained. The document underwent external peer review by reviewers appointed by HRS and each of the collaborating societies, and revisions were made by the chairs.

## Section 2 Arrhythmogenic cardiomyopathy

### 2.1. Arrhythmogenic cardiomyopathy

ACM is defined as an arrhythmogenic heart muscle disorder not explained by ischemic, hypertensive, or valvular heart

CLASS (STRENGTH) OF RECOMMENDATION		LEVEL (QUALITY) OF EVIDENCE‡			
<b>CLASS I (STRONG)</b>	<b>Benefit &gt;&gt;&gt; Risk</b>	<b>LEVEL A</b>	<ul style="list-style-type: none"> <li>High-quality evidence‡ from more than 1 RCTs</li> <li>Meta-analyses of high-quality RCTs</li> <li>One or more RCTs corroborated by high-quality registry studies</li> </ul>		
Suggested phrases for writing recommendations: <ul style="list-style-type: none"> <li>Is recommended</li> <li>Is indicated/useful/effective/beneficial</li> <li>Should be performed/administered/other</li> <li>Comparative-Effectiveness Phrases†:                             <ul style="list-style-type: none"> <li>Treatment/strategy A is recommended/indicated in preference to treatment B</li> <li>Treatment A should be chosen over treatment B</li> </ul> </li> </ul>	<b>CLASS IIa (MODERATE)</b>	<b>Benefit &gt;&gt; Risk</b>	<b>LEVEL B-R (Randomized)</b>	<ul style="list-style-type: none"> <li>Moderate-quality evidence‡ from 1 or more RCTs</li> <li>Meta-analyses of moderate-quality RCTs</li> </ul>	
			<b>LEVEL B-NR (Nonrandomized)</b>	<ul style="list-style-type: none"> <li>Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies</li> <li>Meta-analyses of such studies</li> </ul>	
Suggested phrases for writing recommendations: <ul style="list-style-type: none"> <li>Is reasonable</li> <li>Can be useful/effective/beneficial</li> <li>Comparative-Effectiveness Phrases†:                             <ul style="list-style-type: none"> <li>Treatment/strategy A is probably recommended/indicated in preference to treatment B</li> <li>It is reasonable to choose treatment A over treatment B</li> </ul> </li> </ul>	<b>CLASS IIb (WEAK)</b>	<b>Benefit ≥ Risk</b>	<b>LEVEL C-LD (Limited Data)</b>	<ul style="list-style-type: none"> <li>Randomized or nonrandomized observational or registry studies with limitations of design or execution</li> <li>Meta-analyses of such studies</li> <li>Physiological or mechanistic studies in human subjects</li> </ul>	
			<b>LEVEL C-E0 (Expert Opinion)</b>	Consensus of expert opinion based on clinical experience	
Suggested phrases for writing recommendations: <ul style="list-style-type: none"> <li>May/might be reasonable</li> <li>May/might be considered</li> <li>Usefulness/effectiveness is unknown/unclear/uncertain or not well established</li> </ul>	<b>CLASS III: No Benefit (MODERATE)</b>	<b>Benefit = Risk</b>	<i>(Generally, LOE A or B use only)</i>	<b>LEVEL C-EO (Expert Opinion)</b>	Consensus of expert opinion based on clinical experience
				<b>LEVEL C-E0 (Expert Opinion)</b>	Consensus of expert opinion based on clinical experience
Suggested phrases for writing recommendations: <ul style="list-style-type: none"> <li>Is not recommended</li> <li>Is not indicated/useful/effective/beneficial</li> <li>Should not be performed/administered/other</li> </ul>	<b>CLASS III: Harm (STRONG)</b>	<b>Risk &gt; Benefit</b>			

**Figure 1** ACC/AHA Recommendation System: Applying Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, and Diagnostic Testing in Patient Care.\* Reproduced with permission of the American College of Cardiology and the American Heart Association.<sup>2</sup>

disease. ACM may present clinically as symptoms or documentation of atrial fibrillation, conduction disease, and/or right ventricular (RV) and/or left ventricular (LV) arrhythmia (Figure 2).

The etiology may be part of a systemic disorder (eg, sarcoidosis, amyloidosis), an apparently isolated cardiac abnormality (eg, myocarditis), an infection (eg, Chagas disease), or be genetic (eg, desmosomal arrhythmogenic right ventricular cardiomyopathy [ARVC] or arrhythmogenic left

COR and LOE are determined independently (any COR may be paired with any LOE).

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

\* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

† For comparative-effectiveness recommendations (COR I and IIa; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡ The method of assessing quality is evolving, including the application of standardized, widely used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

ventricular cardiomyopathy [ALVC], lamin A/C, filamin-C, phospholamban) with particular phenotypic (cardiac, cutaneous, immunologic) features (Figure 3). Ion channel disease, which can also cause ACM, is considered in Section 4 Disease Mechanisms and is discussed in other clinical practice documents. Similarly, sarcoidosis and Chagas disease, which are important causes of ACM, are discussed only briefly because they are the subject of other clinical practice documents. In contrast, the arrhythmic management of

**Table 1** Relevant clinical practice documents

Title	Organization	Publication year
2017 AHA/ACC/HRS Guideline for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death <sup>3</sup>	AHA, ACC, HRS	2017
ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities <sup>4</sup>	ACC, AHA, HRS	2008
HRS/EHRA Expert Consensus Statement on the State of Genetic Testing for the Channelopathies and Cardiomyopathies <sup>5</sup>	HRS, EHRA	2011
HRS/EHRA/APHRS Expert Consensus Statement on the Diagnosis and Management of Patients with Inherited Primary Arrhythmia Syndromes <sup>6</sup>	HRS, EHRA, APHRS	2013
2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure <sup>7</sup>	ACC, AHA, HFSA	2016
2013 ACCF/AHA Guideline for the Management of Heart Failure <sup>8</sup>	ACC, AHA	2013
2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure <sup>9</sup>	ESC	2016
Marcus et al. Diagnosis of Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia: Proposed Modification of the Task Force Criteria <sup>10</sup>	NA	2010
Hershberger et al. Genetic Evaluation of Cardiomyopathy—A Heart Failure Society of America Practice Guideline <sup>11</sup>	HFSA	2018
Corrado et al. Treatment of Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia: An International Task Force Consensus Statement <sup>12</sup>	NA	2015

patients with amyloidosis is comprehensively discussed in Section 5.1, since this topic has not been adequately addressed in previous clinical practice documents.

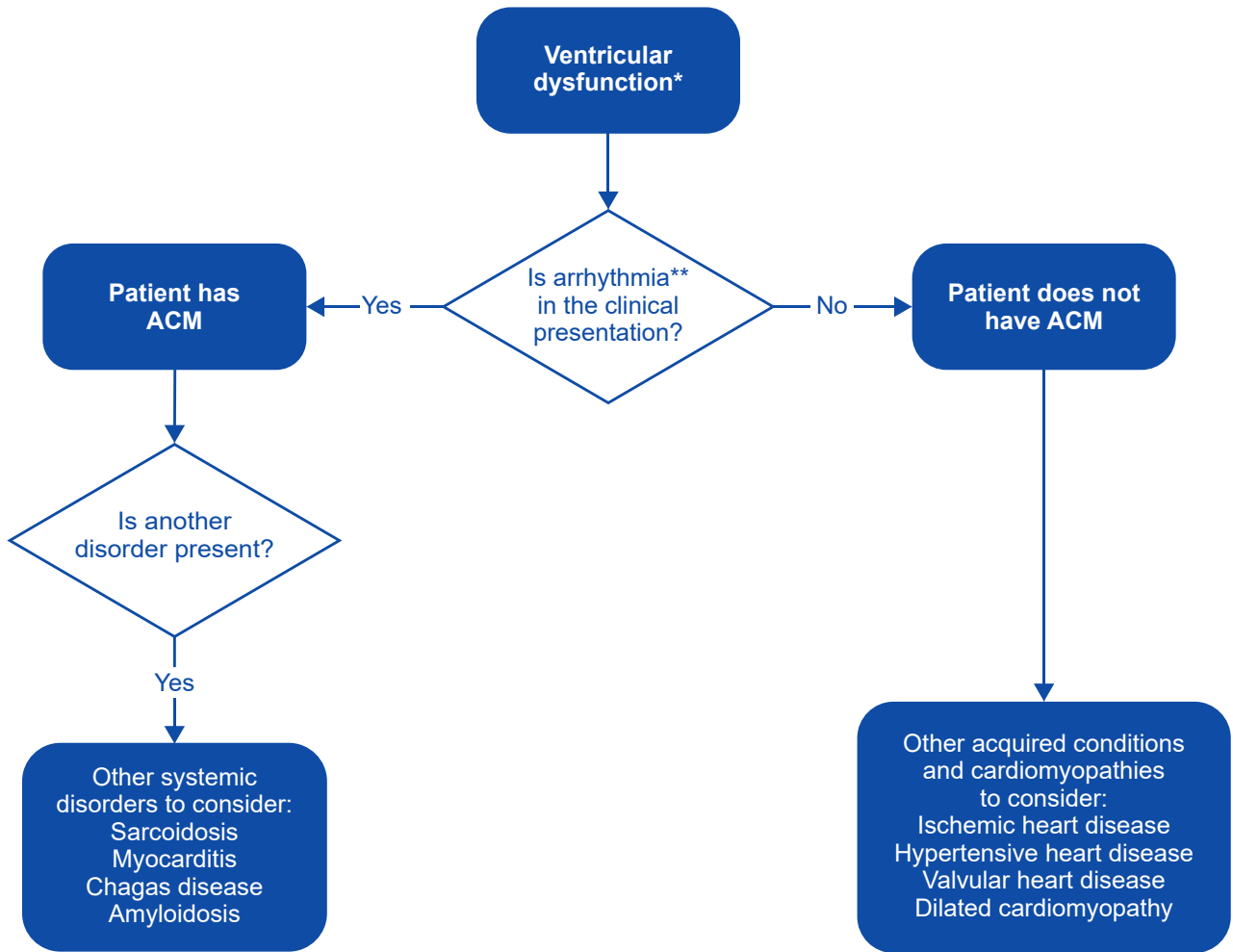
A distinguishing feature of ACM is the clinical presentation with documented and/or symptomatic arrhythmia. The ACM phenotype can overlap with other cardiomyopathies, particularly dilated cardiomyopathy (DCM), in which the arrhythmia presentation may be associated with moderate to severe ventricular dilatation and/or impaired systolic function (eg, ARVC or ALVC caused by DSP, FLNC, SCN5A or PLN variants) (Figure 3 and Figure 4). As with all forms of genetically based cardiovascular disease, the mechanisms responsible for the phenotype that develops rely on dysfunction of final common protein pathways. For instance, DCM is typically caused by variants in genes encoding structural proteins such as cytoskeletal and sarcomeric proteins and, in this case, usually presents with features of heart failure (HF). Arrhythmias, which are most commonly caused by variants in genes encoding ion channels when isolated, may also be a late manifestation in DCM or other forms of cardiomyopathy. These “final common pathways” can interact as overlapping pathways through protein-protein binding and, in these cases, can provide complex phenotypes, such as DCM with significant arrhythmia potential. This distinction between an arrhythmic vs a HF presentation in patients who fulfill current DCM diagnostic criteria is important because the genetic basis, sudden death risk, prognosis, and focus of management are different in these two scenarios. Although rare, ACM can also overlap with hypertrophic cardiomyopathy (HCM; final common pathway, the sarcomere), restrictive cardiomyopathy (RCM; final common pathway, the sarcomere), or LV noncompaction (LVNC; final common pathway, the sarcomere and cytoskeleton). Troponin T variants, unlike other

sarcomeric disease-causing genes, may present with cardiac arrest or sudden death despite mild or even absent LV hypertrophy, whereas troponin I variants may cause a restrictive phenotype in which the dominant clinical presentation is atrial fibrillation.<sup>13–15</sup> Nonsarcomeric HCM (eg, Anderson-Fabry disease), caused by alpha-galactosidase A variants, may also initially present with arrhythmia, though not in the absence of diagnostic phenotypic features.

Clinical evaluation to diagnose and manage ACM in adults and children should consider genetic and nongenetic causes with an assessment of electrocardiographic and structural abnormalities and arrhythmic risk. The pedigree evaluation should include a 3-generation family tree with an emphasis on premature cardiovascular events (eg, sudden death, HF) and associated cardiac (eg, arrhythmias, conduction disease) and noncardiac (eg, skeletal myopathy, renal failure, auditory/visual defects) phenotypes. Mutation analysis, endomyocardial biopsy, and electrophysiology studies (EPSs) are indicated in the particular clinical circumstances discussed below.

## 2.2. Arrhythmogenic right ventricular cardiomyopathy

ARVC is the best characterized of the ACMs, with early clinical reports<sup>16–18</sup> leading to internationally agreed-upon diagnostic<sup>10,18,19</sup> and management guidelines.<sup>12</sup> The predominant RV involvement with left bundle branch block (LBBB) ventricular tachycardia (VT) and fibrous or fibrofatty replacement of RV myocardium is distinct from the LV predominance of most cardiac conditions and other ACMs. ARVC is most often familial, with autosomal dominant inheritance. Studies of one of the uncommon recessive forms<sup>20,21</sup> with a cardiocutaneous phenotype led to the identification of the first disease-causing gene<sup>22</sup> and the



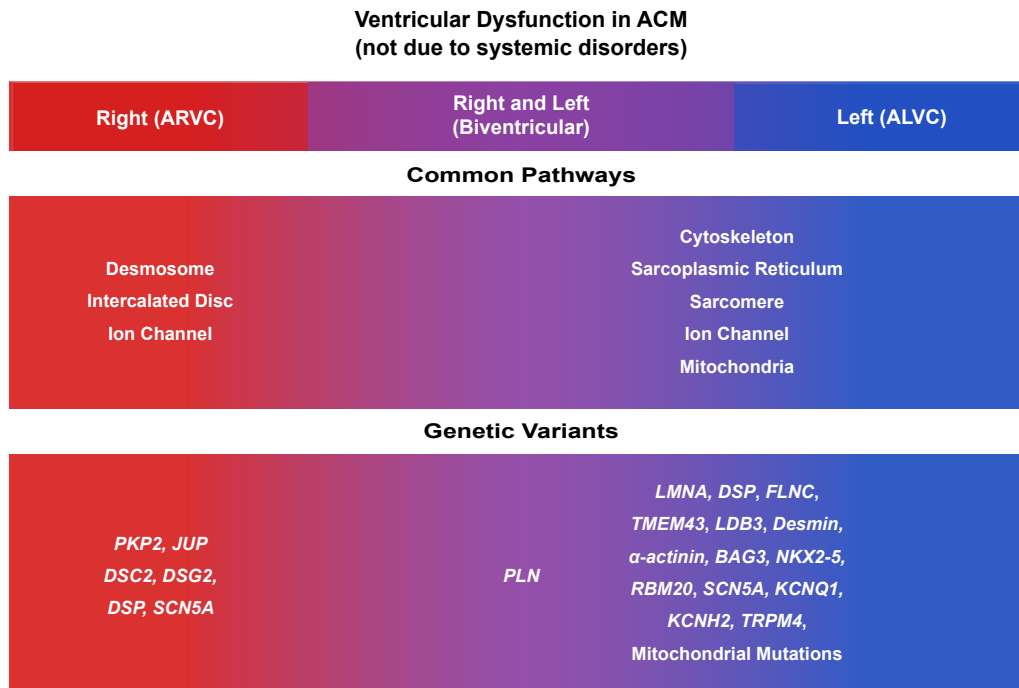
\*Not explained by ischemic, hypertensive, or valvular heart disease

\*\*Arrhythmia includes conduction disease, atrial arrhythmias, ventricular arrhythmias

**Figure 2** Algorithm to consider the presence of an arrhythmogenic cardiomyopathy (ACM).

Genotype	Phenotype
Desmosomal	ARVC/ALVC, hair/skin abnormalities
Lamin A/C	Conduction disease, ventricular arrhythmia/sudden death, DCM, lipodystrophy, muscular dystrophy
SCN5A	Brugada syndrome, conduction disease, AF, VT/VF, DCM
PLN	Low-voltage ECG, VT/VF, DCM, HCM, ARVC
TMEM43	Sudden death M >F, DCM
FLNC	Sudden death, DCM
RBM20	DCM, AF; ventricular arrhythmia/sudden death uncommon as an early feature
Desmin	Skeletal myopathy, DCM; arrhythmia uncommon as an early feature

**Figure 3** Arrhythmogenic cardiomyopathy (ACM): phenotypes associated with the most common genetic causes of ACM. AF = atrial fibrillation; ALVC = arrhythmogenic left ventricular cardiomyopathy; ARVC = arrhythmogenic right ventricular cardiomyopathy; DCM = dilated cardiomyopathy; ECG = electrocardiogram; F = female; *FLNC* = filamin-C; M = male; HCM = hypertrophic cardiomyopathy; *PLN* = phospholamban; *RBM20* = RNA binding motif protein 20; VF = ventricular fibrillation; VT = ventricular tachycardia; *SCN5A* = sodium voltage-gated channel alpha subunit 5; *TMEM43* = transmembrane protein 43.



**Figure 4** Approach to understanding the common pathway and genetic variants in a patient with arrhythmogenic cardiomyopathy (ACM) according to the predominant ventricular dysfunction. See also Table 3. ALVC = arrhythmogenic left ventricular cardiomyopathy; ARVC = arrhythmogenic right ventricular cardiomyopathy; BAG3 = BCL2 associated athanogene 3; DSC2 = desmocollin-2; DSG2 = desmoglein-2; DSP = desmoplakin; FLNC = filamin-C; JUP = junction plakoglobin; KCNH2 = potassium voltage-gated channel subfamily H member 2; KCNQ1 = potassium voltage-gated channel subfamily Q member 1; LDB3 = LIM domain binding 3; LMNA = lamin A/C; NKX2-5 = NK2 homeobox 5; PKP2 = plakophilin-2; PLN = phospholamban; RBM20 = RNA binding motif protein 20; SCN5A = sodium voltage-gated channel alpha subunit 5; TMEM43 = transmembrane protein 43; TRPM4 = transient receptor potential melastatin 4.

recognition that most ARVC is caused by variants in one of several desmosomal genes (see Section 3.8 Genetic Testing, below).<sup>23–26</sup>

Autosomal dominant inheritance predominates and most patients will have one or more pathogenic variants in genes encoding desmosomal proteins. The disease is therefore considered to have desmosome dysfunction as its final common pathway; in other words, ARVC is a disease of the desmosome or desmosomopathy.<sup>27–29</sup> However, there are disease-causing genes that cause “classic” ARVC that do not encode for desmosomal proteins. In most of these cases, the proteins encoded by the mutated gene are either binding partners of desmosomal proteins or proteins whose function is disturbed due to desmosomal protein dysfunction or vice versa, such as ion channels. Recently, pathogenic gene variants have been identified in patients and families, which suggests that more than just the desmosome is involved, but in fact the intercalated disc (ID) as a whole is involved.<sup>27–29</sup> LV ACM would similarly follow this “final common pathway” model.<sup>27–29</sup>

### 2.3. Arrhythmogenic left ventricular cardiomyopathy

The distinctive phenotypic presentation of ARVC with LBBB VT associated with RV structural abnormalities overshadowed recognition that most patients with ARVC develop LV involvement, especially when evaluated with sensitive imaging modalities such as cardiac magnetic

resonance imaging (CMR) (biventricular ACM). With the identification of desmosomal disease-causing variants, individuals and families with predominantly LV arrhythmia and structural abnormalities were recognized<sup>30,31</sup>, as were patients with nondesmosomal arrhythmia-associated variants (eg, lamin A/C,<sup>32</sup> phospholamban,<sup>33</sup> filamin-C<sup>34</sup> who had ACM with predominantly left (but also right) or biventricular phenotypes. The term “ALVC” has been proposed to recognize ACM of LV origin as distinct from ARVC and to rectify the relative lack of diagnostic and prognostic data, which contrasts with multiple international clinical practice documents<sup>10,12,19</sup> generated for ARVC. In time, a better understanding will hopefully be gained of why particular variants (eg, desmosomal, lamin A/C [LMNA], sodium voltage-gated channel alpha subunit 5 [SCN5A], desmin [DES]) cause diverse phenotypes, and the clinical distinction between ARVC and ALVC will be viewed from a pathogenetic rather than a phenotypic basis under an umbrella of genetic and acquired ACM. For the present, however, defining the diagnostic criteria and phenotypic features of ALVC in relation to outcome will be important in understanding the genetic basis and pathogenesis of the genetic and nongenetic conditions encompassed by ACM.

### 2.4. Final common pathways in arrhythmogenic cardiomyopathy

The “final common pathway” hypothesis,<sup>35–37</sup> which states that hereditary cardiovascular diseases with similar



phenotypes and genetic heterogeneity will occur due to abnormalities in genes encoding proteins of similar function or genes encoding proteins participating in a common pathway cascade, was initially described in 1998 in an attempt to direct gene discovery for various cardiovascular clinical phenotypes. Since its original description, the “final common pathway” hypothesis has been fairly predictive of the genes and proteins involved in phenotype development and, to a lesser extent, disease severity. This is seen in HCM (a disease of sarcomere function), arrhythmia disorders such as long QT syndrome (LQTS), Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT), and others (diseases of ion channel function), and Noonan syndrome (a disease of the Ras pathway). In the case of ARVC, the final common pathway appears to be a disturbance of the function of the desmosome and ID. However, ACM includes not only ARVC but also arrhythmogenic left-sided cardiomyopathies, which are currently less well studied. However, data do exist that appear to demonstrate pathways that overlap not only with those associated with ARVC, but also with sarcomere and ion channel pathways. Knowledge of the genes and their encoded proteins involved in the pathophysiology of these disorders, as well as of other proteins that interact with the final common pathway proteins, enables not only a better understanding of the clinical phenotypes that develop but also provides potential targets for current and future therapies (Figure 5 and Figure 18).

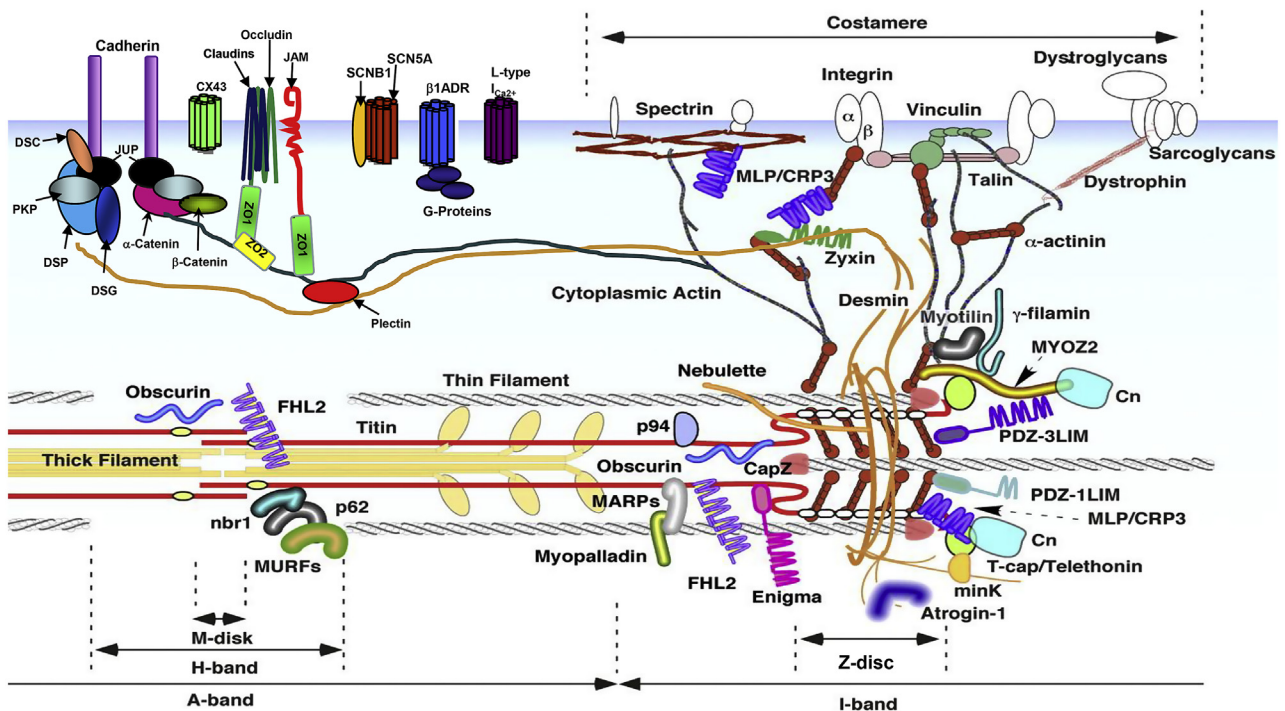
### Section 3 Diagnosis and treatment of arrhythmogenic cardiomyopathy

#### 3.1. Diagnosis of arrhythmogenic cardiomyopathy

The clinical presentation and diagnosis of the genetically determined causes (eg, ARVC, lamin A/C, filamin-C, desmin) of ACM prior to puberty is uncommon. The diagnosis of ACM requires a high degree of clinical suspicion concomitant with diagnostic testing. Clinical perspectives of ACM arise primarily from experiences with patients who present with arrhythmias of RV origin, as well as sudden cardiac death (SCD).<sup>39</sup> In the subset of patients with ARVC, individual clinical and diagnostic findings are individually neither highly specific nor sensitive, and diagnostic criteria have been established to standardize the diagnosis.<sup>10,19</sup> The diagnosis of ARVC should be considered in the following: patients with exercise-related palpitations and/or syncope; survivors of sudden cardiac arrest (particularly during exercise); and individuals with frequent ventricular premature beats (>500 in 24 hours) and/or VT of LBBB morphology in the absence of other heart disease.<sup>10,19,39,40</sup> In patients with suspected ACM who do not meet the diagnostic criteria for ARVC, the evaluation should be systematic to establish the diagnosis of other genetic and nongenetic forms of ACM, with repeated evaluations considered if the disease is strongly suspected.

#### 3.2. Evaluation overview

The underlying principles and clinical evaluations required for the diagnosis and management of ACM are similar in



**Figure 5** Cytoskeletal protein complexes within the cardiomyocyte costamere and Z-disc. Force is distributed externally from the costameres and internally throughout the myocyte by the Z-disc. Structural and signaling proteins within the costamere and Z-disc are shown. Many of these proteins have been implicated in mechano-sensing or sarcomere assembly. MYOZ2 = myozenin 2; Cn = calcineurin; PDZ-3LIM = one-PDZ and three-LIM domain protein; PDZ-1LIM = one-PDZ and one-LIM domain protein; MLP/CRP3 = muscle LIM protein/cysteine-rich protein 3; FHL2 = four-and-a-half LIM protein 2; MARPs = muscle ankyrin repeat proteins; MURFs = muscle-specific ring-finger proteins. Modified with permission of the American Physiological Society.<sup>38</sup>

ARVC and ALVC with respect to excluding acquired causes for the cardiomyopathy, ensuring a probable or definitive diagnosis and characterizing arrhythmia in relation to treatment and prognosis. Genetic causes of isolated or predominantly RV arrhythmia and structural abnormalities are most commonly associated with desmosomal gene variants. There may be additional cutaneous phenotypes that manifest with autosomal dominant *desmoplakin* variants and are often florid in recessive desmosomal disease.<sup>20,23</sup> The genetic causes of arrhythmia and structural disease of LV origin, however, typically manifest with additional cardiac (eg, conduction disease, atrial fibrillation) or systemic (eg, muscular dystrophy, lipodystrophy) phenotypes. Familial evaluation should therefore focus on arrhythmic disease, but also consider associated phenotypes. Several of the ALVC disease-causing gene variants have been reported in patients with LV or biventricular arrhythmia and LV dilatation and/or impaired function (eg, *PLN*, *FLNC*, *LMNA*, *SCN5A*). The diagnostic distinction here is from DCM and its genetic causes.<sup>28,41,42</sup> In ACM, the clinical presentation in the proband and/or family members is typically with arrhythmia rather than HF, although both may be present in advanced disease.

In patients with suspected ACM, the initial evaluation includes clinical history, physical examination, detailed family history, 12-lead electrocardiogram (ECG), 2D echocardiography, ambulatory ECG monitoring, and CMR.<sup>10</sup> Most patients with suspected ACM presenting with arrhythmia can be diagnosed using noninvasive imaging and electrocardiographic assessment. If the initial testing is nondiagnostic, additional testing may include signal-averaged ECG, exercise ECG, pharmacological testing with isoproterenol,<sup>43</sup> endomyocardial biopsy, and EPS. In a series of 48 older children (aged 13–15 years) presenting with possible ACM, a comprehensive clinical and genetic evaluation in the context of the adult Task Force Criteria for the diagnosis of ARVC revealed that 46% of the children had features consistent with a diagnosis of HCM, DCM, or ion channel disease, while 25% had features consistent with ARVC.<sup>44</sup>

The diagnosis of ALVC relies on documenting arrhythmia of isolated or predominantly LV origin in a proband or family member with cardiomyopathy (eg, arrhythmia) not caused by ischemic, valvular, or hypertensive heart disease. Impaired LV function and/or structural abnormalities as determined by 2D ECG and CMR can be absent, mild, or severe. Typically, arrhythmia is an early manifestation of disease. Internationally accepted diagnostic criteria analogous to those established for ARVC<sup>10</sup> are required; however, an issue is the diagnosis of ACM in the presence of other potential causes for which coexistence vs causality may be difficult to determine. Given the currently incomplete knowledge of the genetic basis of ACM, particularly of the ALVC and biventricular forms, the development of clinical diagnostic criteria is needed.

After the original clinical description of RV dysplasia,<sup>17</sup> it became clear that the diagnosis of this condition would be difficult to establish, particularly in the early stages of the disease when RV dilation or segmental dilatation is mild.

Therefore, differentiating RV dysplasia from the normal heart could be equivocal. A task force was subsequently assembled to consider criteria for the diagnosis of arrhythmogenic RV dysplasia/cardiomyopathy, the results of which were published in 1994.<sup>19</sup> The task force concluded that there is no single gold standard for the diagnosis and that disease and the diagnosis require a combination of major and minor criteria encompassing structural, histological, electrocardiographic, arrhythmogenic, and genetic factors. LV disease was excluded from these criteria. The revision of the Task Force Criteria in 2010 included LV disease and added CMR for the diagnosis; the criteria are listed in Figure 6.<sup>10</sup> Diagnostic criteria for ARVC in the pediatric population remain to be established since disease expression in children is uncommon. In a series of 16 patients, clinical presentation was life-threatening arrhythmia in 10 (median age of 14 years). In all 16 patients, LV and/or RV dysfunction was common and associated with the histopathological features of ARVC.<sup>45</sup> Recently, a diagnostic and prognostic role has been proposed for the presence of anti-desmoglein-2 (DSG2) antibodies, which were present in patients with ARVC but not in controls; this work is potentially important and warrants confirmation in a larger number of patients and in other forms of ACM (eg, cardiac sarcoidosis).<sup>46,47</sup>

### 3.3. Family history

A detailed family history covering at least 3 generations and the clinical evaluation of relatives are important in the diagnostic assessment for ACM. In a patient with suspected ACM, a family history focusing on unexplained premature deaths, arrhythmias, and conduction disease may identify familial disease. The presence of associated noncardiac phenotypes (eg, skeletal myopathy, other organ disease) can also provide clues to the underlying diagnosis for both genetic (eg, desmin or lamin myopathy) and nongenetic (eg, Chagas disease) causes.

The 12-lead ECG is an important part of the diagnostic evaluation of patients with suspected ACM. Reports on the ECG findings of patients who meet the diagnostic criteria for ARVC have shown that the majority (>85%) demonstrate at least one characteristic ECG feature of ARVC but a normal ECG has been reported in up to 12%.<sup>49–51</sup> ARVC is a progressive disease, which is reflected in the well-documented dynamic ECG changes associated with disease progression that have been demonstrated in several cohorts of patients with ARVC.<sup>49–54</sup> Over time, the ECG may evolve with further prolongation of the S wave upstroke, increased QRS duration, and development of bundle branch block and precordial T wave inversion (TWI).<sup>53,54</sup>

### 3.4. Electrocardiogram features in arrhythmogenic right ventricular cardiomyopathy

#### 3.4.1. Repolarization abnormalities

The prevalence of TWI in leads V<sub>1</sub>–V<sub>3</sub> (the characteristic ECG finding in patients with ARVC) varies from 19% to 67%,<sup>55–57</sup> presumably due to the difference in study

Modified Task Force Criteria for ARVC – Diagnostic Categories Major and Minor Criteria		
Definite: 2 major OR 1 major and 2 minor, OR 4 minor criteria from different categories		
Borderline: 1 major and 1 minor, OR 3 minor criteria from different categories		
Possible: 1 major, OR 2 minor criteria from different categories		
	Major	Minor
<b>Global or regional dysfunction and structural alterations determined by echo, MRI, or RV angiography:</b>		
Echo	Regional RV akinesia, dyskinesia, or aneurysm and 1 of the following (end diastole): a) PLAX RVOT $\geq 32$ mm (PLAX/BSA $\geq 19$ mm/m <sup>2</sup> ) b) PSAX RVOT $\geq 36$ mm (PSAX/BSA $\geq 21$ mm/m <sup>2</sup> ) c) Fractional area change $\leq 33\%$	Regional RV akinesia, dyskinesia, or aneurysm and 1 of the following (end diastole): a) PLAX RVOT $\geq 29$ mm to $<32$ mm (PLAX/BSA $\geq 16$ to $<19$ mm/m <sup>2</sup> ) b) PSAX RVOT $\geq 32$ to $<36$ mm (PSAX/BSA $\geq 18$ to $<21$ mm/m <sup>2</sup> ) c) Fractional area change $>33$ to $\leq 40\%$
MRI	Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following: a) Ratio RVEDV/BSA $\geq 110$ mL/m <sup>2</sup> (male), $\geq 100$ mL/m <sup>2</sup> (female) b) RVEF $\leq 40\%$	Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following: a) Ratio RVEDV/BSA $\geq 100$ to $<110$ mL/m <sup>2</sup> (male), $\geq 90$ to $100$ mL/m <sup>2</sup> (female) b) RVEF $>40$ to $\leq 45\%$
RV angiography	Regional RV akinesia, dyskinesia, or aneurysm	
<b>Tissue characterization of wall</b>		
Endomyocardial biopsy showing fibrous replacement of the RV free wall myocardium in $\geq 1$ sample, with or without fatty replacement and with:	Residual myocytes $<60\%$ by morphometric analysis (or $<50\%$ if estimated)	Residual myocytes 60% to 75% by morphometric analysis (or 50% to 65% if estimated)
<b>Repolarization abnormalities</b>		
ECG	Inverted T waves in right precordial leads (V <sub>1</sub> , V <sub>2</sub> , and V <sub>3</sub> ) or beyond in individuals $>14$ years of age (in the absence of complete RBBB QRS $\geq 120$ ms)	I. Inverted T waves in leads V <sub>1</sub> and V <sub>2</sub> in individuals $>14$ years of age (in the absence of complete RBBB) or in V <sub>4</sub> , V <sub>5</sub> , or V <sub>6</sub> . II. Inverted T waves in leads V <sub>1</sub> , V <sub>2</sub> , V <sub>3</sub> and V <sub>4</sub> in individuals $>14$ years of age in the presence of complete RBBB
<b>Depolarization/conduction abnormalities</b>		
ECG	Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V <sub>1</sub> to V <sub>3</sub> )	I. Late potentials by SAECG in $\geq 1$ of 3 parameters in the absence of QRS duration of $\geq 110$ ms on the standard ECG: a) Filtered QRS duration (fQRS) $\geq 114$ ms b) Duration of terminal QRS $<40$ $\mu$ V (low-amplitude signal duration) $\geq 38$ ms c) Root-mean-square voltage of terminal 40 ms $\leq 20$ $\mu$ V II. Terminal activation duration of QRS $\geq 55$ ms measured from the nadir of the S wave to the end of the QRS, including R' in V <sub>1</sub> , V <sub>2</sub> , or V <sub>3</sub> in the absence of complete RBBB
<b>Arrhythmias</b>		
	Nonsustained or sustained VT of LBBB with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL)	I. Nonsustained or sustained VT or RV outflow configuration, LBBB morphology with inferior axis (positive QRS in II, III and aVF and negative in lead aVL) or of unknown axis II. $>500$ ventricular extrasystoles per 24 hours (Holter)
<b>Family history</b>		
	I. ARVC confirmed in a first-degree relative who meets current Task Force Criteria II. ARVC confirmed pathologically at autopsy or surgery in a first-degree relative III. Identification of a pathogenetic mutation categorized as associated or probably associated with ARVC in the patient under evaluation	I. History of ARVC in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current Task Force Criteria II. Premature sudden death ( $<35$ years of age) due to suspected ARVC in a first-degree relative III. ARVC confirmed pathologically or by current Task Force Criteria in second-degree relative

**Figure 6** Modified Task Force Criteria for arrhythmogenic right ventricular cardiomyopathy (ARVC) showing the diagnostic categories for major and minor criteria according to the 2010 ARVC Task Force Criteria. These criteria are sensitive and specific in differentiating patients with ARVC from control populations but have not been adequately tested in relation to other arrhythmogenic cardiomyopathies (ACMs) with overlapping phenotypes (eg, cardiac sarcoidosis, myocarditis).<sup>48</sup> BSA = body surface area; ECG = electrocardiogram; echo = echocardiogram; MRI = magnetic resonance imaging; PLAX = parasternal long-axis; PSAX = parasternal short-axis; RBBB = right bundle branch block; RV = right ventricular; RVEDV = right ventricular end-diastolic volume; RVEF = right ventricular ejection fraction; RVOT = right ventricular outflow tract; SAECG = signal-averaged electrocardiogram; VT = ventricular tachycardia.

populations. TWI in the precordial leads beyond  $V_2$  is relatively common in Afro-Caribbean individuals,<sup>58</sup> although it is rare (1% in females and 0.2% in males) in asymptomatic white individuals.<sup>59</sup> TWI in patients younger than 14 years of age is more frequently observed in athletes (the so-called juvenile pattern).<sup>60</sup> TWI is reasonably specific in patients older than 14 years of age and is considered a major diagnostic abnormality in ARVC. TWI in leads  $V_1$ – $V_4$  in individuals older than 14 years associated with complete right bundle branch block (CRBBB) is a minor criterion for the diagnosis of ARVC (Figure 7). The presence of TWI in lateral and/or inferior leads suggests LV involvement in patients with ARVC (Figure 7).<sup>61</sup>

### 3.4.2. Depolarization and conduction abnormalities

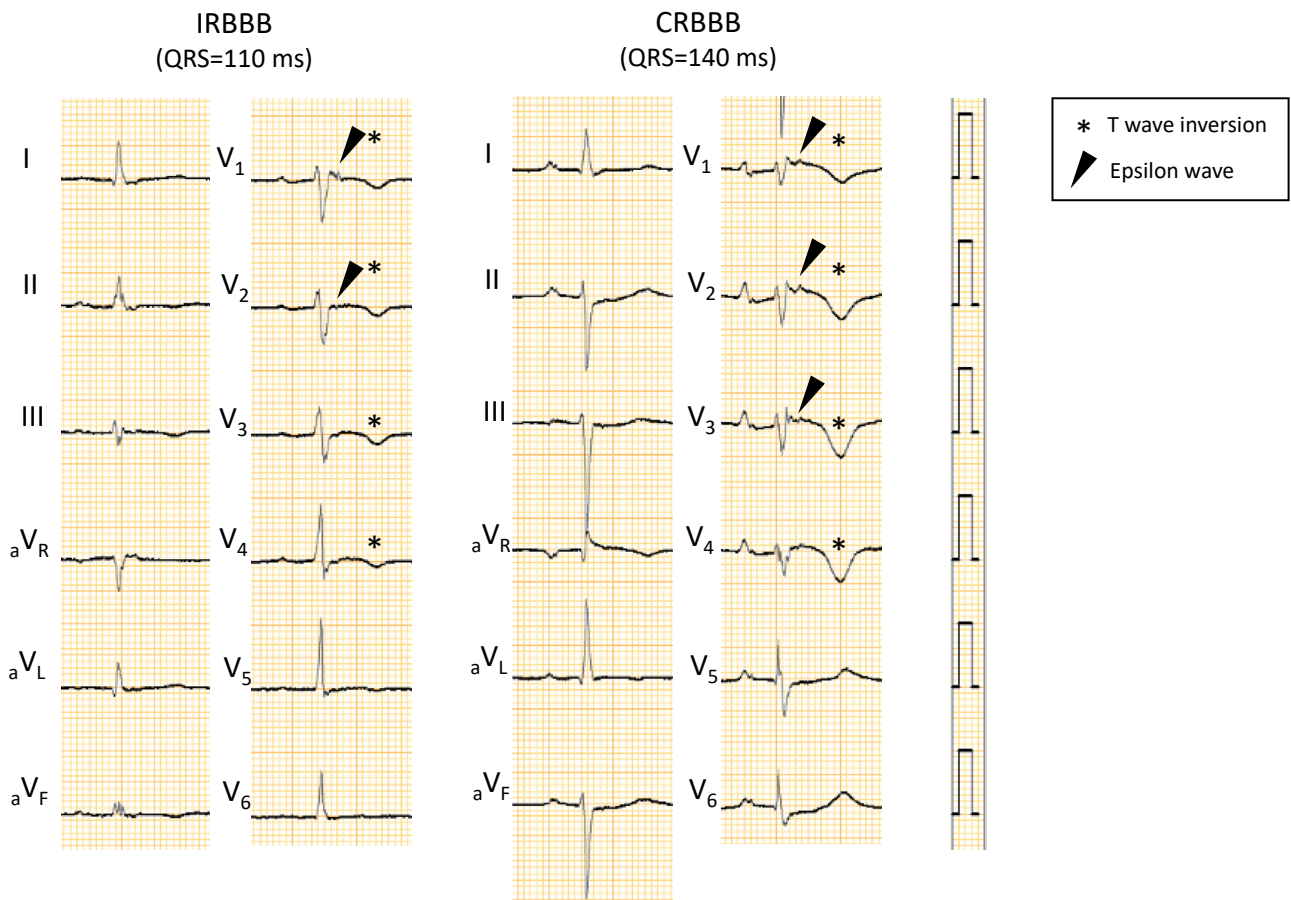
#### 3.4.2.1. Epsilon wave

The epsilon wave is defined as a reproducible low-amplitude deflection located between the end of the QRS and the onset of the T wave in leads  $V_1$ – $V_3$  (Figure 7).<sup>10,56</sup> Epsilon waves reflect delayed conduction in the RV (Figure 7). The prevalence of the epsilon wave in European and American registries varies from 0.9% to 25%.<sup>62</sup> Electroanatomical mapping in patients with ARVC and an

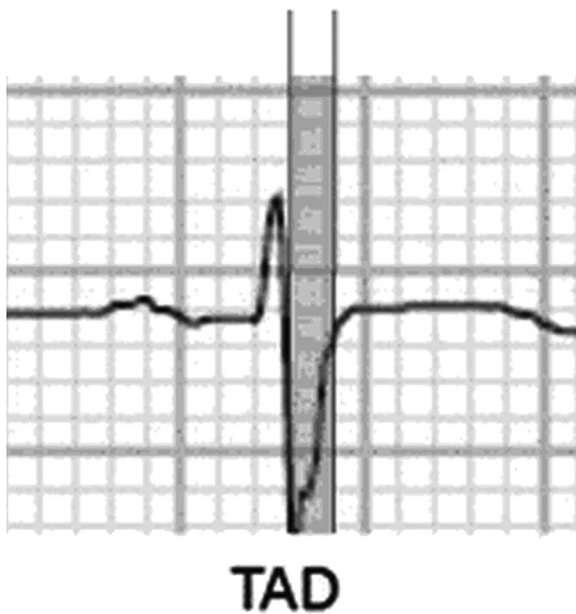
epsilon wave has shown that the timing of the epsilon wave on the surface ECG corresponded to activation of the basal (peri-tricuspid) RV region of the epicardium. Epsilon waves have been associated with severe conduction delay due to extensive endocardial and epicardial scarring at that site.<sup>63</sup> Epsilon waves may reflect short-term arrhythmia risk but are of limited diagnostic utility because they are variable, have low sensitivity and specificity (seen in other conditions), and are dependent on ECG filter setting and magnification.<sup>54,62,64,65</sup>

#### 3.4.2.2. Prolonged terminal activation duration

Prolonged terminal activation duration (TAD) is measured from the nadir of the S wave to the end of all depolarization deflections (Figure 8). A TAD  $\geq 55$  ms in any of the  $V_1$ – $V_3$  leads in the absence of CRBBB is defined as a prolonged TAD.<sup>55,66</sup> Prolonged TAD in leads  $V_1$ – $V_3$  has been reported to aid in differentiating ARVC from right ventricular outflow tract (RVOT)-VT.<sup>67</sup> Prolonged TAD was confirmed in 30 of 42 patients with ARVC and in only 1 of 27 patients with idiopathic RVOT-VT.<sup>55</sup> Moreover, TAD prolongation was the sole ECG abnormality in 4 of 7 gene-positive family members with ARVC,<sup>68</sup> suggesting a role in the early recognition of “at-risk” individuals.



**Figure 7** Representative 12-lead electrocardiogram (ECG) obtained from patients with arrhythmogenic right ventricular cardiomyopathy (ARVC) with incomplete right bundle branch block (IRBBB) and complete right bundle branch block (CRBBB). QRS duration of IRBBB and CRBBB was 110 ms and 140 ms, respectively. The closed arrow indicates an epsilon wave, which was defined as low-amplitude deflection located between the end of the QRS and the onset of the T wave in leads  $V_1$ – $V_3$ . The asterisk indicates the T wave inversion recorded in  $V_1$ – $V_4$  in patients with ARVC and IRBBB or CRBBB.



**Figure 8** Terminal activation duration (TAD) is measured from the nadir of the S wave to the end of all depolarization deflections and is prolonged if  $\geq 55$  ms in any of the  $V_1$ – $V_3$  leads in the absence of complete right bundle branch block (CRBBB). Modified with permission of Oxford University Press on behalf of the European Society of Cardiology.<sup>69</sup>

### 3.4.3. Electrocardiogram abnormalities in arrhythmogenic cardiomyopathies other than arrhythmogenic right ventricular cardiomyopathy

Characterization of ECG findings in other ACMs is less detailed. The 12-lead ECG abnormalities include inverted T waves in leads I, aVL, and  $V_4$ – $V_6$ ; other repolarization abnormalities; generalized low-voltage; increased QRS duration; and isolated ectopy of LV origin. A completely normal ECG is uncommon. Variants in *lamin A/C* may be associated with progressive conduction disease (eg, PR prolongation to atrioventricular [AV] block), variants in desmosomal genes and *phospholamban* with a low voltage ECG, and in *filamin-C* with minor repolarization changes only. In contrast to ARVC associated with desmosomal variants, ECG abnormalities do not appear to be an early marker of disease in FLNC and desmin-related ACM. In ACMs associated with systemic disease, conduction abnormalities are often early features (eg, sarcoidosis and Chagas disease).<sup>70,71</sup>

### 3.4.4. Ambulatory electrocardiogram monitoring

Ambulatory ECG monitoring (24 to 48 hours) is important for characterizing all patients for whom the diagnosis of ACM is being considered. The presence of  $>500$  ventricular premature beats per 24-hour monitoring period is a minor diagnostic criterion for ARVC. In a study of 40 patients meeting ARVC Task Force Criteria who underwent ambulatory ECG monitoring for an average of 159 hours, the average ventricular premature beat count (per 24 hours) was 1091, with significant day-to-day variation. Despite this variation, the 24-hour burden was accurate 89.6% of the time to the correct grouping based on the revised Task Force Criteria.<sup>72,73</sup>

Documentation of ventricular arrhythmia with a morphology consistent with an LV origin is required for the diagnosis of ALVC. Precise definitions relating to characteristics VT and/or frequency of ventricular ectopy remain to be established for forms of ACM other than ARVC. The arrhythmia may be asymptomatic or associated with palpitations and/or impaired consciousness.

### 3.4.5. Signal-averaged electrocardiogram

Although an abnormal signal-averaged ECG was a minor criterion in the 2010 Task Force Criteria, its use has declined largely due to its limited sensitivity and specificity, as well as its limited availability in many medical centers.<sup>10,74</sup>

## 3.5. Cardiac imaging

Echocardiography and other noninvasive imaging modalities are important for evaluating patients suspected of ACM to assess structural and functional abnormalities and aid in diagnosis.<sup>75,76</sup>

For many patients with suspected ACM, 2D echocardiography provides adequate visualization, enabling a systematic qualitative and quantitative assessment of ventricular function and cavity dimensions, although there may be limitations when imaging the RV. Additional imaging with CMR provides accurate measurements of volumes and also regional and global ventricular function.<sup>52</sup> If CMR is contraindicated or not available, multidetector computed tomography (CT), RV angiography or radionuclide angiography are alternatives, but are currently less frequently used to assess ventricular function. The Task Force Criteria for ARVC include the presence of RV akinesia, dyskinesia, or aneurysms, together with an assessment of RVOT diameter and RV-fractional area change. Emerging echocardiographic parameters in the evaluation of patients with suspected or established ARVC include the measurement of tricuspid annular plane systolic excursion, RV basal diameter, global longitudinal strain (RV and LV), mechanical dispersion (RV and LV), and the use of 3D echocardiography.<sup>77,78</sup> However, prospective studies are needed before these assessments are recommended for routine use.

The 2010 Task Force Criteria for ARVC included CMR parameters for RV global and regional dysfunction and RV volume.<sup>10</sup> The major criterion requires a regional RV wall motion abnormality and either increased RV end-diastolic volume ( $\geq 110$  mL/m<sup>2</sup> in men;  $\geq 100$  mL/m<sup>2</sup> in women) or depressed right ventricular ejection fraction (RVEF)  $\leq 40\%$  (sensitivity: men 76%, women 68%; specificity: men 90%, women 98%). The CMR minor criterion also requires regional RV wall motion abnormality with lesser degrees of RV enlargement ( $\geq 100$  mL/m<sup>2</sup> in men;  $\geq 90$  mL/m<sup>2</sup> in women).<sup>10</sup> The Task Force Criteria did not include CMR measures of RV myocardial fat or late gadolinium enhancement (LGE); however, these were not considered reliable measurements at the time the Task Force Criteria were developed (2010).

The 2010 Task Force Criteria for ARVC do not define diagnostic criteria for LV involvement. If present, LGE is

typically found in a subepicardial or mid-wall distribution confined to the LV. LV dominant disease may be underdiagnosed and attributed to other disorders.<sup>78</sup> The potential of CMR to diagnose and risk stratify patients with ACM remains to be fully exploited. LV LGE has been identified as the sole imaging abnormality in patients with desmoplakin disease who have arrhythmia of LV origin and a normal ECG.<sup>31</sup> In general, ECG abnormalities and arrhythmia are considered the earliest manifestations<sup>54,79</sup>; however, Sen-Chowdhry et al have also demonstrated that CMR may be sensitive to detecting early changes in ARVC. The role of CMR in the early diagnosis of ACM of nondesmosomal origin, for other genetic and acquired causes, warrants evaluation.<sup>30,80</sup> CMR expertise will be particularly important in the early diagnosis in the absence of ECG or other imaging abnormalities, given the risk that epicardial fat may be misinterpreted as delayed enhancement.

LV structural and functional abnormalities will relate to particular genetic abnormalities and disease stage. Current genotype-phenotype relations are based on small data sets but suggest that ACM with clinically significant LV arrhythmias (eg, ALVC) may occur with “normal” to severely impaired LV function. Experience is greatest with lamin A/C disease, in which phenotypes include Emery-Dreifuss muscular dystrophy, generalized lipodystrophy, DCM with HF, progressive conduction disease with late-onset DCM, and ALVC with or without significant LV impairment. ALVC caused by *desmoplakin* variants can also be present with absent to severe LV dysfunction and may present with sudden death.<sup>81</sup> Preliminary experience indicates that LGE on CMR can be present in the absence of LV dysfunction and may provide an early diagnostic feature when LV arrhythmia appears to have occurred in isolation.<sup>31</sup>

### 3.6. Electrophysiology testing

Electrophysiology testing in ACM is often unnecessary for the diagnostic evaluation of patients with suspected ARVC or ALVC.<sup>12</sup> Multicenter studies of patients with ARVC who received an implantable cardioverter defibrillator (ICD) have demonstrated the low predictive accuracy of electrophysiology testing in identifying those at risk of SCD and/or life-threatening arrhythmia.<sup>82,83</sup> The reported incidence of “life-saving” ICD discharges for treatment of fast VT/ventricular fibrillation (VF) was not significantly different between those who were and those were not inducible. Corrado et al studied 106 patients with ARVC who received an ICD as primary prevention. The positive and negative predictive value for VT/VF inducibility was 35% and 70%, respectively.<sup>82</sup> Electrophysiology testing, however, may be beneficial in patients with refractory ventricular arrhythmias for ablation consideration and differentiation from RVOT tachycardia. In this setting, electrophysiology testing with high-dose isoproterenol may help differentiate patients with idiopathic VT or ventricular premature beats from those with ARVC.<sup>84</sup>

### 3.7. Endomyocardial biopsy

Biopsy can be particularly useful in identifying systemic or inflammatory conditions that cause ACM (eg, sarcoidosis, myocarditis). However, endomyocardial biopsy (one of the Task Force Criteria for the diagnosis of ARVC) is invasive, lacks sensitivity and specificity, has low diagnostic yield, and, therefore, is now rarely performed in the initial diagnosis of ARVC. The characteristic histological feature is the presence of transmural fibrofatty replacement of the RV myocardium, with major and minor criteria differentiated by degree of replacement (<60% vs 60%–75% myocytes by morphometric analysis).<sup>10</sup> Diagnosis by biopsy is limited due to false negatives secondary to patchy involvement and sampling error.<sup>85,86</sup> Electroanatomical voltage mapping may improve the yield of endomyocardial biopsy by identifying areas of low voltage.<sup>87</sup> Endomyocardial biopsy is associated with the risk of perforation, which is increased with RV free wall biopsy.<sup>85,88</sup> Septal biopsy is generally not helpful because it is typically the least affected area of the myocardium in ARVC.<sup>86</sup> Novel immunohistochemical analysis in patients with ARVC with desmosomal variants demonstrated altered plakoglobin and connexin43 signal as a marker of disease expression<sup>79,89–91</sup>; however, this has not proven to be of diagnostic utility. Sarcoidosis, for which treatment may include steroids, is important in the differential diagnosis of ARVC, but similar limitations with regard to sampling error and risk are present. Myocardial tissue obtained from postmortem and explanted hearts will have the value but not the limitations of endomyocardial biopsy and should be sought and examined whenever feasible.

### 3.8. Genetic testing

General concepts on the role of genetic testing in the diagnosis and management of ARVC and other ACMs are outlined below, with recommendation flow diagrams shown in [Figure 10](#) and [Figure 11](#).

#### 3.8.1. Genetic testing methods

Several methods are available to identify the genetic basis of an ACM. Single genes are usually analyzed by Sanger sequencing, which has been proven to be a reliable technique to identify variants underlying genetic disease and has been the gold standard for decades. With increasing numbers of genes identified as underlying a specific cardiac disorder (genetic heterogeneity) and the fact that more than one gene and/or variant (digenic inheritance or polygenic inheritance) can contribute to the disease phenotype,<sup>75,92</sup> next-generation sequencing (NGS)-based methods enable the parallel sequencing of several targeted genes (a panel, eg, cardiomyopathy-panel) at the same time and at relatively low cost.<sup>93</sup> In addition to these targeted NGS panels, sequencing of all protein coding genes (exome) of the human genome (whole exome sequencing [WES]) or even all DNA nucleotides (whole genome sequencing [WGS]) can be performed.

### 3.8.2. Variant and gene interpretation

DNA sequences normally vary in the general population when comparing different individuals. However, even when they reside in bona fide ACM-susceptibility genes, not every DNA variant contributes to the disease.<sup>94</sup> The major challenge is to correctly assign potential pathogenicity to these DNA variants. The American College of Medical Genetics and Genomics (ACMG) has published guidelines for interpreting genetic variants and proposed a classification based on the likelihood that a variant is related to disease (Table 2): pathogenic (class 5), likely pathogenic (class 4), uncertain significance (class 3), likely benign (class 2), or benign (class 1), in which a “likely pathogenic” and “likely benign” variant are used to mean greater than 90% certainty of a variant being either disease-causing or benign, respectively.<sup>95</sup>

The importance of correctly interpreting an identified variant’s pathogenicity is now considered the most critical step in genetic testing, especially considering that there appears to be substantial interviewer disagreement over variant interpretation.<sup>97–100</sup> Ethnicity information is essential for interpreting the data.<sup>101</sup> Within the ACMs, examples of incorrect classification of variants in major ARVC-related genes have been published.<sup>102–106</sup> Besides variant adjudication and the vexing variant of uncertain significance (VUS), many alleged and published ACM-susceptibility genes are being re-analyzed as to the strength of their disease-gene association and, over time, several published ACM-susceptibility genes may be demoted to genes of uncertain significance. Accordingly, when evaluating patients suspected of an ACM, it is critical that the genetic tests conducted as part of the evaluation and the interpretation of the genetic test results be conducted by comprehensive teams with expertise in these disorders.<sup>107</sup>

Several genes have been implicated in ACM, with varying evidence strength (Table 3). The ClinGen Cardiovascular Clinical Domain Working Group for cardiovascular disorders is curating genes in relation to specific disorders.<sup>108</sup> One of the first efforts in adapting the ACMG 2015 guidelines for variant interpretation in genes related to cardiogenetic disease has recently been published, and this process is also underway for ACM.<sup>109</sup>

Depending on the reason for using the results of a genetic test, a certain amount of evidence for pathogenicity is neces-

sary; for prenatal diagnostics or a pre-implantation genetic diagnosis, the evidence for pathogenicity must be strong, and only class 5 variants are used. For genetic cascade screening in family members, only class 4 and 5 variants are used; family members negative for the family’s class 5 variant are dismissed from regular cardiologic follow-up, whereas those relatives who test negative for a given family’s class 4 variant remain in the cardiogenetic clinics, albeit for longer follow-up intervals. The frequency and duration of follow-up for family members who are negative for a class 4 variant should be individualized at the discretion of the clinical team. Class 3 variants (ie, a VUS) should be deemed “nonactionable.” Given both incomplete penetrance and age-dependent penetrance, clinically unaffected family members should not be tested to determine their status for a class 3 variant found in the family unless additional evidence (such as various functional validation assays and/or demonstration of co-segregation among clinically affected family members) has been obtained that would prompt a variant promotion from an ambiguous class 3 variant (VUS) to a clinically actionable class 4 or class 5 variant.

### 3.8.3. Which test to use

With the availability of NGS, the number of genes that can be studied in a single patient rapidly increases. However, the value of including a greater number of genes in a panel should be weighed against the drawback of adding genes that have insufficient evidence (or none) of being related to the patient’s disease or that account for only a small percentage of the genotyped patients and are therefore more prone to errors in attributing the pathogenic role of the identified variants.

Therefore, a list of core genes can focus on those with sufficient evidence to be disease-related. The ClinGen working group for cardiovascular disorders is responsible for reviewing clinical, genetic, and experimental data to establish the strength of evidence supporting gene-disease associations in heart disease. Gene curation for HCM was recently completed, and curation for ARVC and DCM is underway.<sup>110,111</sup> Until the official ClinGen-approved results of these gene curation efforts are available, we anticipate that the genes listed in Table 3 will likely be retained as ACM-susceptibility genes with sufficient evidence to merit their disease-gene association and will be useful in clinical practice. These recognized genes should therefore be prioritized for patients and families with a clinical diagnosis of ACM or its subforms. If other genes are included in the analysis, identifying a pathogenic or likely pathogenic variant in one of the non-ACM related genes should not automatically or reflexively be considered an explanation for the patient’s ACM phenotype. In other words, a pathogenic or likely pathogenic variant in *KCNH2* (a gene in which P/LP variants cause abnormalities in the QTc without structural heart disease) does not carry the same intrinsic probability of pathogenicity for ACM as a plakophilin-2 (PKP2) variant that has been graded as a pathogenic or likely pathogenic variant.

**Table 2** Classification of likelihood of pathogenicity of a variant

Classification of variant	Description	Likelihood of being pathogenic
Class 5	Pathogenic	>95%
Class 4	Likely pathogenic	>90%
Class 3	Variant of uncertain significance	10–90%
Class 2	Likely benign	<10%
Class 1	Benign	<5%

Adapted from Plon et al.<sup>96</sup>

**Table 3** Minimum set of genes to be prioritized in arrhythmogenic cardiomyopathy (ACM)

Gene	Protein type	Predominant type of mutation	OR/EF <sup>100</sup>	Signal: Background <sup>94</sup>	Remarks	References
<i>BAG3</i>	Chaperone	Truncating and missense	NA	NA	Also causes myofibrillar myopathy	121
<i>DES</i>	IF	Truncating and missense	NA	NA	Also causes myofibrillar myopathy	122
<i>DSC2</i>	Desm	Truncating and missense	NT 2.15 (EF 0.53); T 21.5* (EF 0.95)	ns	Rare	26
<i>DSG2</i>	Desm	Truncating and missense	NT 2.83* (EF 0.65) T 19.8* (EF 0.95)	2:1* (NT/T)	Rarely recessive	123
<i>DSP</i>	Desm	Truncating and missense	NT 2.1* (EF 0.52) T 89.9* (EF 0.99)	ns	Recessive: Carvajal syndrome	23,124
<i>FLNC</i>	Actin crosslink	Truncating and missense	NA	NA	Also causes myofibrillar myopathy	34
<i>JUP</i>	Desm	Missense	NT 7.8* (EF 0.87) T 28.1 (EF -)	NA	Recessive: Naxos syndrome	22,125
<i>LDB3</i>	Z-band	Missense	NA	NA	Cypher/ZASP	126
<i>LMNA</i>	NE	Truncating and missense	NA	NA	AV block; CD	127
<i>NKX2-5</i>	Homeobox	Truncating and missense	NA	NA	AV block, CD, CHD	128
<i>PKP2</i>	Desm	Truncating	NT 1.3 (EF 0.23) T 484.7* (EF 1.0)	10:1* 42:1*	Large deletions 1-2%	24
<i>PLN</i>	Ca	Missense, nonsense, and deletion	NA	NA	Predominantly R14del	33,129
<i>RBM20</i>	Splice factor	Missense	NA	NA	Mostly in exon 9	130
<i>SCN5A</i>	Sodium channel	Mostly missense	NA	NA	Brugada, SND, CD	131
<i>TMEM43</i>	NE	Missense	NT 0.76 (EF-) T 13 (EF-)	ns	p.S358L disease-causing; also called LUMA	132

These genes have multiple lines of evidence indicating involvement in ACM and its subtypes (arrhythmogenic left ventricular cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy). OR/EF and Signal:Background data are largely derived from cohorts with western European ancestry, and other ethnicities can be different.

AV = atrioventricular; BV = biventricular; Ca = calcium handling; CD = conduction delay; CHD = congenital heart disease; CPVT = catecholaminergic polymorphic ventricular tachycardia; *DES* = desmin; Desm = desmosomal; *DSC2* = desmocollin-2; *DSG2* = desmoglein-2; EF = etiological fraction; IF = intermediate filament; LD = left dominant; NA = data not available; NE = nuclear envelope; ns = not significant; NT = nontruncating variants; OR = odds ratio; RD = right dominant; SND = sinus node dysfunction; T = truncating variants.

\*Genes with significant excess in cases over ExAc reference samples.<sup>100</sup> Other genes that have been identified in ACM with insufficient or conflicting evidence are *ABCC9*,<sup>112</sup> *TGFB3*,<sup>113</sup> *TTN*,<sup>114</sup> *CTNNA3*,<sup>115</sup> sarcomeric genes (*MYH7*, *MYBPC3*),<sup>116,117</sup> *SCN3B*,<sup>117</sup> *CDH2*,<sup>118,119</sup> *TJP1*.<sup>120</sup>

A recent viewpoint paper by the European Society of Cardiology (ESC) working group on myocardial and pericardial diseases emphasized that, in a diagnostic setting, only recognized genes associated with the condition should be investigated in patients who meet the diagnostic criteria of a specific cardiovascular condition. WES and WGS should be used for genetic diagnosis only if filtered against recognized disease-causing genes. The coverage should enable the identification of all exonic variants in these genes.<sup>107</sup>

### 3.8.4. Advantages and disadvantages of various methods

The various techniques that can be used for genetic testing each have their own advantages and disadvantages, as summarized in Table 4. Coverage of the genomic regions of interest, the possibility of identifying large deletions/duplications, flexibility, and costs are important factors to consider when ordering a genetic test.

Sanger sequencing is a reliable method with good coverage of the nucleotides that need to be studied,

**Table 4** Different methods for screening genes

	Target	Coverage	CNVs	Flexibility	Costs
Sanger sequencing	Single gene(s)	++	--	-	IE
Targeted NGS panel	Panel of genes of interest	+	+	-	+/-
WES filtered against genes of interest	Set of genes of interest	+/-	+/-	+	+
WES	All genes	+/-	+/-	+	+
WGS	All genes and intronic sequences	+	+	+	++

CNVs = copy number variations; IE = inefficient (expensive for large amounts of sequencing but inexpensive for a small amount); NGS = next-generation sequencing; WES = whole exome sequencing; WGS = whole genome sequencing; ++ = very high; + = high; +/- = intermediate; - = low; -- = very low.



particularly for evaluating a single or a small number of genes. Sanger sequencing is also appropriate for cascade testing in at-risk family members, clinical confirmation of research genetic results, and cosegregation studies. However, large deletions and duplications of genes can be missed when using Sanger sequencing. It is well known that larger deletions and/or duplications (eg, in *PKP2*) are a known cause of ACM<sup>68,133,134</sup> and can be identified in a small percentage of cases.

Targeted NGS panels have the advantage that they are well validated, and it is well known which parts are insufficiently covered. Additional Sanger sequencing experiments are frequently used to evaluate the insufficiently covered regions.<sup>93</sup> Bioinformatic tools must be added to

the bioinformatics pipeline to identify deletions and/or duplications in the genes of interest in targeted panel screening, a relatively inexpensive, fast, and reliable method to study larger series of genes.

The results of exome sequencing, a relatively fast test, can be filtered against the set of core genes rather than evaluating all 20,000+ human genes. This reduces the chance of incidental findings. The major advantage of exome sequencing is that novel or additional genes can be easily added by “opening” the data whenever new disease genes are established. On the downside, the quality and/or coverage of some parts of the “core genes” may be insufficient, and larger deletions and/or duplications can easily be missed.

### 3.8.5. Who to study

COR	LOE	Recommendations	References
I	C-EO	<b>For individuals and decedents with either a clinical or necropsy diagnosis of ACM, genetic testing of the established ACM-susceptibility genes is recommended.</b>	
I	C-EO	<b>For genetic testing of the established ACM-susceptibility genes, comprehensive analysis of all established genes with full coverage is recommended.</b>	

A genetic test is generally performed in an index patient with either a clinical diagnosis that fulfills the clinical criteria for the disease in question or when there is at least a reasonable index of suspicion for that specific disorder. Both the selected disease gene panel and the subsequent genetic test interpretation should be strongly influenced by the veracity of the phenotype. The genetic testing of patients with nonspecific syncope or TWIs confined to only precordial lead V1, for example, should be strongly discouraged.<sup>135</sup> When interpreting a genetic test, the available evidence that a specific gene is related to ACM should be taken into account. The test used should be of sufficient quality to identify variants in these genes. This may entail additional tests to cover all exons and additional bioinformatic and laboratory tests to identify deletions and duplications.

For individuals who have died suddenly with a postmortem (likely) diagnosis of ACM or one of its subforms, postmortem genetic testing should again include those disease genes implicated in the necropsy diagnosis. Various sources to isolate DNA can be used, such as blood, frozen tissue, fibroblasts from a skin biopsy, and even formalin-fixed paraffin-embedded tissue.<sup>136,137</sup>

ACM-associated genes can also be evaluated in autopsy-negative SCD cases because ventricular arrhythmias leading to SCD may precede structural abnormalities.<sup>138</sup>

Table 3 lists the minimum set of genes to be evaluated.

### 3.8.6. The role of genetic testing in arrhythmogenic cardiomyopathies

A positive genetic test result (ie, likely pathogenic, class 4 or pathogenic variant, class 5) can (1) genetically confirm the clinical diagnosis and provide disease–gene-specific risk stratification and tailoring of therapies<sup>139</sup> and (2) enable variant-specific cascade genetic testing of appropriate family members and relatives (see Section 3.9 Cascade Family Screening), including the potential for prenatal or preimplantation genetic diagnostics (a topic beyond the scope of this consensus statement).

In the current Task Force Criteria for ARVC,<sup>10</sup> the “Identification of a pathogenic mutation categorized as associated or probably associated with ARVC in the patient under evaluation” is weighted as a **major** criterion

in the “family history” section. A pathogenic mutation (now classified as either a class 4 or class 5 variant per ACMG nomenclature) is defined as “a DNA alteration associated with ARVC that alters or is expected to alter the encoded protein, is unobserved or rare in a large non-ARVC control population, and either alters or is predicted to alter the structure or function of the protein or has demonstrated linkage to the disease phenotype in a conclusive pedigree.” Since a positive genetic test result is regarded as a major criterion, it will contribute up to 50% to the diagnosis of ARVC, thus highlighting the importance of an experienced genetic team. Nevertheless, there is the question of whether to put this much weight on a genetic result for which the true characteristics such as penetrance are generally not well known.

### 3.8.7. The use of a genetic test in risk stratification and management

Whether the result of a genetic test can be used for risk stratification or management depends on the known relationship between genotype and phenotype. In general, there is limited evidence for a clinically actionable relationship between genotype and phenotype, with a few exceptions presented in the following subsections.

#### 3.8.7.1. Left ventricular dysfunction

LV dysfunction is most often present in patients with ACM with pathogenic or likely pathogenic variants in *LMNA*, *BAG3*, or one of the founder variants in the *PLN* and *TMEM43* genes, followed by variants in *DSP*, *DSG2/DSC2* and the lowest frequency in *PKP2/JUP*. This holds true for both index patients and family members.<sup>140,141</sup>

#### 3.8.7.2. Multiple variants

Approximately 3%–6% of patients have more than 1 pathogenic or likely pathogenic variant contributing to the disease phenotype. Patients with multiple pathogenic variant-mediated ACM have more severe disease, as reflected by an earlier age at disease onset<sup>92</sup> and the presence of VTs (<20 years vs 35 years for patients with a single ACM-causative variant),<sup>68</sup> a higher lifetime risk of arrhythmia<sup>142</sup> or SCD,<sup>143</sup> and earlier progression to cardiomyopathy.<sup>141,144,145</sup>

#### 3.8.7.3. Specific variants and genes

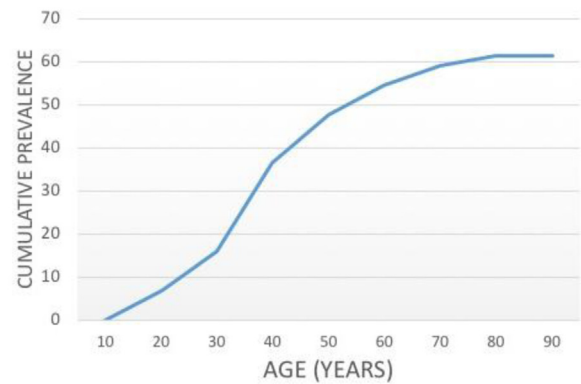
##### 3.8.7.3.1. Desmosomal genes

Disease expression reaching diagnostic criteria is most common between 20 and 50 years of age (40%; 95% CI, 34%–46%),<sup>146</sup> although in one series, 9 of 40 pediatric desmosomal gene-positive patients had the disease at a mean age of  $17.8 \pm 5.1$  years.<sup>147</sup> LGE identified by CMR, most frequently seen in the LV myocardium, was the first evidence of disease expression in a small subset of individuals.<sup>75</sup> In a comprehensive evaluation of 274 family members, the incidence of a new diagnosis (as per 2010 Task Force Criteria) in those aged 10–20 years was 0.5 per 100 person-years, and the odds ratio of a diagnosis in those aged <18 years in the multivariate analysis was 0.37 (0.14–0.93), with no diagnosis reached under the age of 14 years. Likewise, a new diagnosis in relatives older than 60 years is less common.<sup>146</sup> The cumulative prevalence by decade is shown in Figure 9 based on data from Quarta et al.<sup>147</sup>

Overall, relatives have less severe disease compared with probands, are more commonly asymptomatic, and show disease onset at an older age.<sup>145</sup> Arrhythmic events in family members appear to occur only in the presence of manifest electrocardiographic and structural changes.<sup>146,148</sup> Similar enhanced disease activity is observed in pediatric probands compared with their age-matched relatives.<sup>75</sup>

##### 3.8.7.3.1.1. Desmoplakin (*DSP*)

Pathogenic variants in *DSP*-encoded desmoplakin are associated with a spectrum of disorders, including cutaneous syndromes. For patients with likely pathogenic (class 4) or pathogenic (class 5) variants in *DSP* over



**Figure 9** Cumulative prevalence of disease expression in family members at risk of arrhythmogenic right ventricular cardiomyopathy (ARVC).<sup>147</sup>

50% of index-patients and 17% of family members have an arrhythmic phenotype with LV dysfunction (Table 2).<sup>141</sup> In addition to biventricular forms, left dominant forms are also present and extensive fibrotic patterns can be identified by CMR (see Section 5.5 Left Ventricular Noncompaction).<sup>140,158</sup>

##### 3.8.7.3.2. Lamin A/C (*LMNA*)

The cardiac phenotype for *LMNA*-mediated ACM is characterized by atrial fibrillation and cardiac conduction disease, which can precede the development of ventricular arrhythmias and cardiomyopathy by decades.<sup>149,150</sup> *LMNA* variants have also been identified in patients diagnosed with ARVC<sup>151–153</sup> or more biventricular and left-dominant forms of the disease.<sup>127,154</sup> Risk stratification has been reported from Asian and European populations.<sup>155,156</sup> In the European study, nonsustained ventricular tachycardia (NSVT), left ventricular ejection fraction (LVEF) <45% at first clinical contact, male sex, and nonmissense variants have been reported to be risk factors for malignant ventricular arrhythmias.<sup>156</sup> Patients with a *LMNA* variant who are in need of a pacemaker often receive an ICD, which is effective in treating possibly lethal tachyarrhythmias.<sup>157</sup>

##### 3.8.7.3.3. Transmembrane protein 43 (*TMEM43*)

The p.S358L mutation in transmembrane protein 43 (*TMEM43*) is a specific founder variant that has been identified in a large number of patients diagnosed with ARVC from Europe and Canada (Newfoundland).<sup>132,159</sup> Its clinical phenotype is characterized by poor R wave progression in precordial leads and LV enlargement in 43% of affected individuals, with 11% meeting the criteria for DCM.<sup>160</sup> A study involving nearly 150 p.S358L-*TMEM43*-positive individuals concluded that survival was greater for those treated with an ICD than for those with conventional, non-ICD care.<sup>160</sup>

##### 3.8.7.3.4. Phospholamban (*PLN*)

The pathogenic p.R14del-*PLN* variant has been identified in 1% of patients with ARVC in the United States and 12% of Dutch patients with ARVC,<sup>33</sup> as well as in patients from

several other countries (Spain, Germany, Greece, Canada, Norway). Patients with this variant frequently have low-voltage ECGs and are considered to be at high risk for

malignant ventricular arrhythmias and end-stage HF, with LVEF <45% and sustained VT or NSVT as independent risk factors (see Section 5.4 Phospholamban).<sup>161</sup>

3.8.8. Limitations of genetic testing

COR	LOE	Recommendations	References
IIa	C-EO	<b>The interpretation of a cardiac genetic test by a team of providers with expertise in genetics and cardiology can be useful.</b>	

Performing a genetic test on an index patient or relative has several aspects that must be considered and thus requires a comprehensive, expert team. There are specific test-related “technical” aspects that result in some variants not being detected by certain tests (see Section 3.8.4 Advantages and Disadvantages of Various Methods). The interpretation of a genetic test requires an accurate interpretation of variants. For example, class 1, 2, and 3 variants are not considered as actionable. The interpretation is also influenced by the pretest probability, which depends greatly on the precise clinical characterization of the phenotype. Additionally, the identification of a genetic defect does not necessarily predict the disease severity in that specific individual. When using a panel with more genes that underlay other phenotypes, incidental findings may be identified, such as likely pathogenic or pathogenic variants (class 4 and 5) that could lead to a different phenotype than the one that motivated the referral.

Genetic testing can cause a mixture of positive and negative emotions for the patient. Genetic counselors can help patients and their families navigate these feelings and learn to live with this inherited condition. Genetic counselors can explain the implications of identified genetic variants in ways that alleviate anger, anxiety, fear, and guilt that are likely to occur in patients and their families.

This expert team should therefore consist, at minimum, of cardiologists, clinical and molecular geneticists, genetic counselors, and pathologists, or individuals with expertise that encompass these subspecialties.

The ACMG has issued an updated list of over 50 actionable genes.<sup>162</sup> Laboratories performing WES or WGS (generally for diagnostic odyssey cases) should report the presence of pathogenic or likely pathogenic variants residing in these genes, unless the individual who is being tested has chosen not to receive these results. This list includes 5 of the established ARVC-susceptibility genes. For these incidental findings, however, the frequency of related clinical phenotypes in unselected patient populations is generally not well established. When variants in a known ARVC-susceptibility gene are identified in the context of a nonphenotype-driven incidental finding, the likelihood that this variant (even if graded as a class 4 or 5) portends

the presence of ARVC or the risk of developing ARVC in the future is considered low, as was recently established for arrhythmia and ARVC-related genes.<sup>98,163</sup>

3.9. Cascade family screening

See Evidence Table: Cascade Family Screening. Flow diagram of recommendations is shown in Figure 11.

3.9.1. Cascade family screening: screening recommendations in children and adults

Clinical cascade testing refers to the cardiovascular and genetic evaluation of first-degree family members of an individual (proband) with a confirmed diagnosis of ACM and is ideally performed within the confines of a multidisciplinary cardiovascular genetics program, familiar with the clinical and genetic complexities of the condition.<sup>164</sup> The underlying etiology of ACM in many cases is due to alterations in cardiac genes that encode proteins critical to normal heart development and/or function. For the most part, these are inherited as an autosomal-dominant trait, such that first-degree family members have a 50% a priori risk of developing ACM, although the penetrance and disease severity are typically less in family members compared with probands.<sup>145</sup> Detailed clinical and genetic familial evaluation, both at the time of diagnosis and during follow-up, will help determine the inheritance patterns and likelihood of consanguinity.

Desmosomal variants are relatively common in control populations and may erroneously be considered disease-causing,<sup>94</sup> although certain variants have a well-recognized association with the condition, and targeted genetic testing can be used in isolation within specific families.

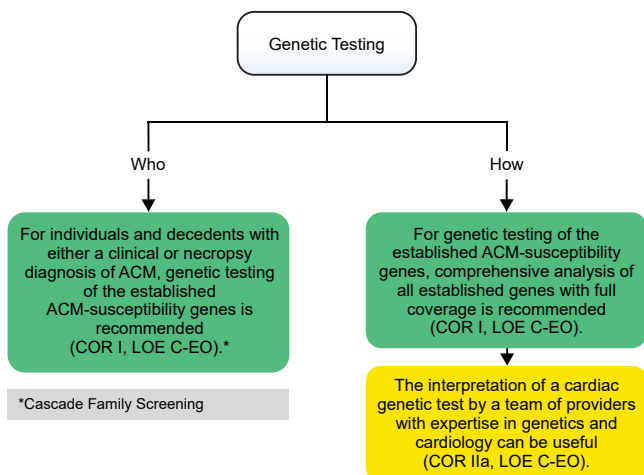


Figure 10 Genetic testing recommendations. \* = Cascade family screening: see Section 3.9 Cascade Family Screening. ACM = arrhythmogenic cardiomyopathy; COR = Class of Recommendation; LOE = Level of Evidence. Colors correspond to COR in Figure 1.

## 3.9.1.1. Family history

COR	LOE	Recommendations	References
I	C-EO	<b>It is recommended that a genetic counselor or appropriately experienced clinician obtain a comprehensive 3-generation family history.</b>	

A detailed  $\geq 3$ -generation family history collected from the proband at their initial consultation is vital and should be obtained by a genetic counselor or an appropriately experienced clinician.<sup>165–168</sup> The family history can be used to determine the existence of familial disease, provide important data regarding the full phenotypic spectrum within the family, and identify relatives who should be informed of the need for cardiac evaluation.

## 3.9.1.2. Cardiac evaluation

The yield of cardiac screening is highly varied due to age-related and typically incomplete penetrance, and the disease spectrum can be diverse, even within families harboring the

same variant, incorporating right-sided, left dominant, and biventricular phenotypes. Family members may display a relatively mild or incomplete phenotype, including subtle electrocardiographic or structural abnormalities.

## 3.9.1.3. Age-related penetrance of disease in at-risk relatives

COR	LOE	Recommendations	References
I	B-NR	<b>It is recommended that first-degree relatives undergo clinical evaluation every 1–3 years starting at 10–12 years of age.</b>	34,75,146, 160,161, 169,170

ACM variants can display incomplete penetrance and varied expression. In ARVC there is age-related penetrance with onset typically observed in the third and fourth decade of life, although this may vary with the underlying etiology and specific familial characteristics. Disease expression is, however, recognized in adolescents, although it is extremely rare under the age of 10 and is almost exclusively seen in probands.<sup>75,145,171</sup> At-risk relatives who undergo clinical evaluation may be clinically affected, have borderline disease (incomplete penetrance), or be clinically unaffected. Serial evaluation can define ongoing disease expression and risk stratification.<sup>50,147</sup> In a study of families with ARVC, the highest probability of a diagnosis of ARVC occurred between 20–50 years of age (40%; 95% CI, 34%–46%).<sup>146</sup>

COR	LOE	Recommendations	References
I	B-NR	<b>Cardiovascular evaluation should include 12-lead ECG, ambulatory ECG, and cardiac imaging.</b>	21,75,145–147, 172–174

Evaluation of all at-risk family members should include a 12-lead ECG, 24-hour Holter monitoring, and cardiac imaging. The exact imaging modality (echocardiogram, CMR, or CT) can vary depending on availability and institutional expertise. A study of relatives harboring a *PKP2* causal variant identified in the proband showed that approximately one-third had a diagnosis of ARVC, one-third had borderline disease, and one-third were unaffected,<sup>172</sup> although other studies have shown a much lower diagnostic rate among family members.<sup>173</sup> In relatives who demonstrate disease features, electrocardiographic changes typically occur earlier and more commonly than structural changes,<sup>174</sup> although subtle structural abnormalities can be identified by detailed echocardiographic analysis.<sup>77,175</sup> LGE on CMR, most frequently observed in the LV myocardium, was the first evidence of disease expression in a small subset.<sup>75</sup>

## 3.9.1.4. Cascade cardiac investigations

COR	LOE	Recommendations	References
IIb	C-LD	<b>Exercise stress testing (arrhythmia provocation) may be considered as a useful adjunct to cardiovascular evaluation.</b>	148

In addition, exercise stress testing may expose a latent phenotype by initiating ventricular ectopy or arrhythmia.<sup>148</sup> Symptoms such as syncope or palpitations should initiate an urgent evaluation.

3.9.1.5. Cascade genetic testing

When a likely pathogenic or pathogenic genetic variant has been identified in the proband, cascade genetic testing can be offered to first-degree at-risk relatives. Cascade genetic testing should only be offered in the context of comprehensive pretest genetic counseling, with the goal to discuss the process of genetic testing; the implications of the results for patients and their family members; social, lifestyle, and insurance implications; and an examination of patients' feelings about either a positive or negative result.<sup>166,176</sup> Inappropriate use of genetic testing in a family has the potential to introduce unnecessary worry and fear, as well as potential harms related to the misinterpretation of genetic variants.<sup>166,176</sup> Cascade genetic testing is therefore

only offered to family members where a likely pathogenic or pathogenic variant in a known disease-associated gene is identified in the proband and can be interpreted with an appropriate level of expertise. Consideration must also be given to the family members' psychosocial wellbeing.

Efforts to ensure ongoing reclassification of variants are critically important for cascade genetic testing and families benefit from being managed in a specialized multidisciplinary cardiac genetic service. Ideally, systematic processes or a combined approach of relying on new information from the testing laboratories and review of family variants triggered by a family member returning for routine follow-up should be in place.

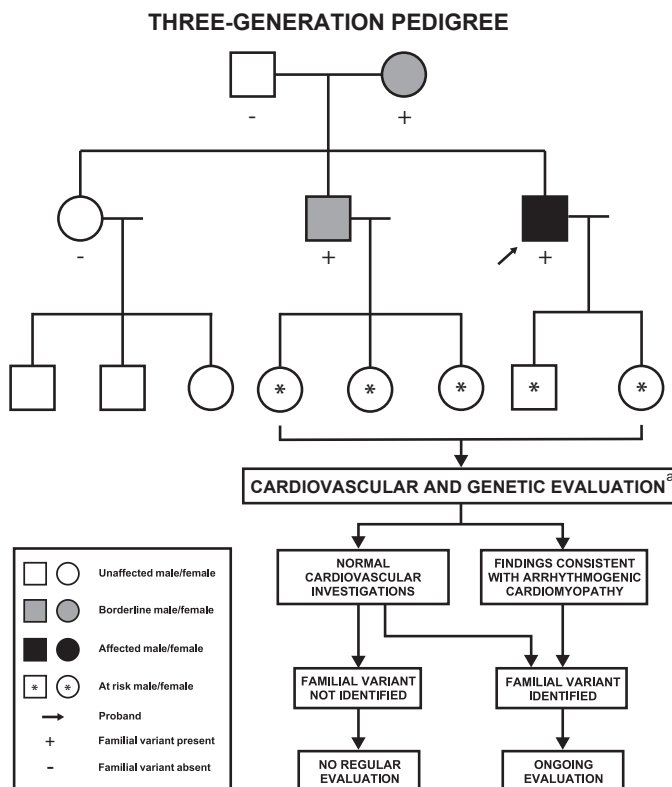
COR	LOE	Recommendations	References
I <b>ib</b>	C-EO	<b>In families with a variant classified as pathogenic, it may be reasonable for asymptomatic members of a family who do not have the familial variant and have a normal cardiovascular evaluation to be released from regular screening and educated to return if disease symptoms occur.</b>	

At present, the key role of genetic testing for many ACM conditions is to identify asymptomatic carriers who can be targeted for closer surveillance or gene-negative relatives who are unlikely to develop disease and can be released from future screening.<sup>169</sup> Comprehensive cardiovascular and genetic investigation will also help confirm variant status within the wider family. Family members who are comprehensively evaluated and who do not carry the pathogenic variant may be released from further regular evaluation, although they should be educated regarding specific symptoms and advised to seek further evaluation should these occur.

3.9.1.6. Cascade genetic testing in minors

Cascade testing for familial variants in children remains controversial, given the complex medical, legal, and psychological issues involved. Testing is typically deferred until an age when

clinical features are more likely, although this can be affected by the clinical disease spectrum and segregation of the variant in other family members, coupled with the specific preferences of the child and family. Genetic testing should always be guided



It is recommended that a genetic counselor or appropriately experienced clinician obtain a comprehensive 3-generation family history (COR I, LOEC-EO).

It is recommended that first-degree relatives undergo clinical evaluation every 1–3 years<sup>b</sup> starting at 10–12 years of age<sup>c</sup> (COR I, LOE B-NR).

Cardiovascular evaluation should include 12-lead ECG, ambulatory ECG, and cardiac imaging (COR I, LOE B-NR).

Exercise stress testing (arrhythmia provocation) may be considered as a useful adjunct to cardiovascular evaluation (COR I**ib**, LOE C-LD).

In families with a variant classified as pathogenic, it may be reasonable for asymptomatic members of a family who do not have the familial variant and have a normal cardiovascular evaluation to be released from regular screening and educated to return if disease symptoms occur (COR I**ib**, LOE C-EO).

a. The use of genetic testing assumes prior identification of a pathogenic variant in the proband.  
 b. May vary with age, lifestyle, and family history.  
 c. Unless family history of disease suggests potential for earlier onset or presence of pathogenic variant in family supports presymptomatic genetic testing.

**Figure 11** Summary of family screening recommendations. COR = Class of Recommendation; ECG = electrocardiogram; LOE = Level of Evidence. Colors correspond to COR in Figure 1.

by the child's best interest and performed by a multidisciplinary team including specialist cardiologists, geneticists, genetic counselors, and psychologists with expertise in genetic counseling, variant interpretation, and disease management, when feasible.

### 3.10. Risk stratification and implantable cardioverter defibrillator decisions

See Evidence Table: Risk Stratification and ICD Decisions. The recommendation flow diagram is shown in [Figure 12](#).

SCD is the most feared consequence of ACM. In a series of SCD occurrences in young individuals, ARVC accounts for up to 20% of the cases, particularly in certain genetic ethnic populations. There are fewer data on the contribution of other ACMs to SCD, likely a result of the difficulty of diagnosing these diseases postmortem. Prevention of SCD is possible with ICDs; identifying patients at risk of SCD is necessary to target those who should receive ICDs.

Risk stratification is limited by the available data, nearly all of which are retrospective in nature and obtained from patients referred to tertiary care centers. Also, some of the larger, more recent registry data almost certainly contain patients who were previously reported in prior publications from the same center. Thus, the largest, most recent registries are the most reliable in terms of risk assessment.

Most series include patients with ICDs; in fact, in some series an ICD is a requirement for entry into the registry.

Appropriate therapies for VT, ventricular flutter (VFL), and VF are included as endpoints. ICD-treated arrhythmias are used as a surrogate for SCD, but there is abundant evidence that not all ICD-treated arrhythmias would have led to SCD. To make the SCD endpoint more specific and detailed, a number of studies have the separate endpoints of potentially life-threatening arrhythmias and all ventricular arrhythmias. In these studies, life-threatening arrhythmias are generally defined as SCD or hypotensive VT in patients without ICDs and ICD-treated VF or VFL  $\geq 240$  bpm in those with ICDs. All arrhythmias are generally defined as any sustained arrhythmia ( $>30$  seconds) that spontaneously occurs and any ventricular arrhythmia treated by the ICD, including treatment with antitachycardia pacing or shock. Some registries include cardiovascular death, heart transplantation, and ventricular arrhythmias for a composite endpoint. An international collaboration of 18 centers from Europe and North America developed a risk model,<sup>177</sup> where male sex, relative youth, ECG, imaging features reflecting more extensive RV disease, and the severity of ventricular arrhythmia were the most accurate identifiers of the high-risk cohort studied. The model provides 1- to 5-year ventricular arrhythmia event-free survival rates for the predicted high-risk group and the potential to determine 5-year risk in the individual patient.

COR	LOE	Recommendations	References
I	C-EO	<b>The decision to implant an ICD in an individual with ACM should be a shared decision between the patient and the physician, taking into account the risks and benefits of the ICD over the potential longevity of the patient.</b>	

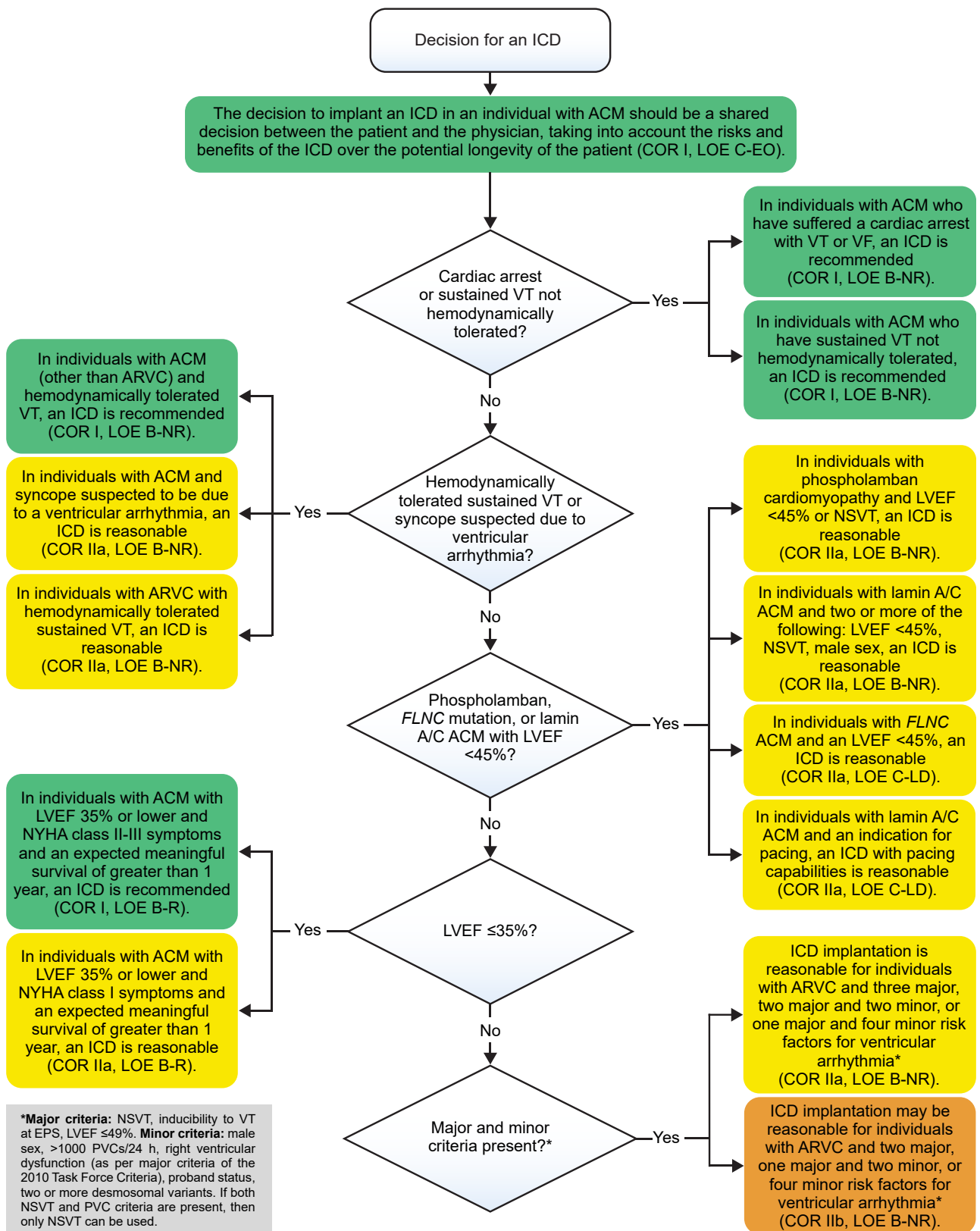
A shared decision-making process is essential to clarify the anticipated benefits of an ICD for each individual patient. Potential options for therapy and the evidence supporting them are discussed to enable patients to make an informed decision.

COR	LOE	Recommendations	References
I	B-NR	<b>In individuals with ACM who have suffered a cardiac arrest with VT or VF, an ICD is recommended.</b>	83,178–182
I	B-NR	<b>In individuals with ACM who have sustained VT not hemodynamically tolerated, an ICD is recommended.</b>	83,178–180, 182

As with other diseases, previous sustained ventricular arrhythmia is undoubtedly the strongest predictor of recurrent ventricular arrhythmia. Cohort studies that included patients with ARVC and ventricular arrhythmic (VT or VF) events prior to enrollment have shown that these arrhythmic events are a strong predictor of future life-threatening ventricular arrhythmias; an ICD can therefore be a life-saving device.<sup>83,178–180</sup>

COR	LOE	Recommendations	References
IIa	B-NR	<b>In individuals with ACM and syncope suspected to be due to a ventricular arrhythmia, an ICD is reasonable.</b>	82,83,178–180, 183–189

Syncope is a common symptom in young individuals, and it is important to clarify that syncope is likely due to a ventricular arrhythmia. In cohort studies, syncope is an independent predictor of future ventricular arrhythmic events.<sup>82,83,178–180,183,184</sup> In the Pavia Registry, 73 of 301 patients followed for a mean of 5.8 years had a clinical outcome of SCD, aborted SCD, syncopal VT or electrical storm, or cardiovascular mortality,<sup>183</sup> with a history of syncope being an independent predictor (hazard ratio [HR]: 4.38;  $P = .002$ ). In the Hopkins Registry, 186 of 312 patients followed for  $8.8 \pm 7.3$  years had a clinical outcome of VT or VF with syncope as a univariate predictor (HR: 1.85;  $P = .021$ ).



**Figure 12** Implantable cardioverter defibrillator (ICD) recommendations. See Section 5 Other Disorders for recommendations regarding left ventricular non-compaction. ACM = arrhythmogenic cardiomyopathy; ARVC = arrhythmogenic right ventricular cardiomyopathy; COR = Class of Recommendation; EPS = electrophysiology studies; FLNC = filamin-C; LOE = Level of Evidence; LVEF = left ventricular ejection fraction; NSVT = nonsustained ventricular tachycardia; NYHA = New York Heart Association; PVC = premature ventricular contraction; VF = ventricular fibrillation; VT = ventricular tachycardia. Colors correspond to COR in Figure 1.

COR	LOE	Recommendations	References
<b>IIa</b>	<b>B-NR</b>	<b>In individuals with ARVC with hemodynamically tolerated sustained VT, an ICD is reasonable.</b>	178–180,183

Hemodynamically tolerated VT has also been associated with adverse arrhythmic outcomes. In the Pavia registry, 73 of 301 patients followed for a mean of 5.8 years had a clinical outcome of SCD, aborted SCD, syncope, VT or electrical storm, or cardiovascular mortality.<sup>183</sup> Hemodynamically tolerated monomorphic VT was an independent predictor (HR: 2.19;  $P = .023$ ). In the Hopkins registry, VT at presentation was a univariate predictor for VT (HR: 1.86;  $P < .001$ ).

COR	LOE	Recommendations	References
<b>IIa</b>	<b>B-NR</b>	<b>ICD implantation is reasonable for individuals with ARVC and three major, two major and two minor, or one major and four minor risk factors for ventricular arrhythmia.*</b>	179,180,183,190
<b>IIb</b>	<b>B-NR</b>	<b>ICD implantation may be reasonable for individuals with ARVC and two major, one major and two minor, or four minor risk factors for ventricular arrhythmia.*</b>	179,180,183,190

\*Major criteria: NSVT, inducibility to VT at EPS, LVEF  $\leq 49\%$ . Minor criteria: male sex,  $>1000$  premature ventricular contractions (PVCs)/24 hours, RV dysfunction (as per major criteria of the 2010 Task Force Criteria, see Figure 6), proband status, 2 or more desmosomal variants. If both NSVT and PVC criteria are present, then only NSVT can be used.

The variables associated with VT/VF in more than one cohort include younger age at presentation (significant in 4 series)<sup>83,179,180,190</sup> and male sex (significant in 2 series).<sup>183,190</sup> The variables associated with VT/VF in only one study include NSVT,<sup>82</sup> PVC frequency  $>1000/24$  hours,<sup>180</sup> VT inducibility at EPS,<sup>180</sup> atrial fibrillation,<sup>183</sup> hemodynamically tolerated monomorphic VT,<sup>183</sup> participation in strenuous exercise,<sup>183</sup> and reduced LVEF.<sup>83</sup>

COR	LOE	Recommendations	References
<b>I</b>	<b>B-R</b>	<b>In individuals with ACM with LVEF 35% or lower and NYHA class II-III symptoms and an expected meaningful survival of greater than 1 year, an ICD is recommended.</b>	182,185–188,191

ACM can be secondary to a wide variety of genetic defects and acquired abnormalities. Some may have structural and functional abnormalities that overlap with DCM. Etiologies are more likely to present early in their clinical course with ventricular arrhythmias, particularly the inherited cardiomyopathies caused by pathogenic variants in *PLN*, *LMNA*, *FLNC*, *TMEM43*, *RBM20*, and *DES*. In large randomized controlled trials that enrolled patients with DCM, ICDs improved survival. Patients enrolled in these trials had New York Heart Association (NYHA) class II or III symptoms and were undergoing guideline-directed medical therapy for HF.

COR	LOE	Recommendations	References
<b>IIa</b>	<b>B-R</b>	<b>In individuals with ACM with LVEF 35% or lower and NYHA class I symptoms and an expected meaningful survival of greater than 1 year, an ICD is reasonable.</b>	187

The Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial included patients with nonischemic DCM and NYHA I symptoms, comprising 99 of 458 patients who were randomized to an ICD vs medical therapy for the prevention of SCD.

COR	LOE	Recommendations	References
<b>I</b>	<b>B-NR</b>	<b>In individuals with ACM (other than ARVC) and hemodynamically tolerated VT, an ICD is recommended.</b>	156,161
<b>IIa</b>	<b>B-NR</b>	<b>In individuals with phospholamban cardiomyopathy and LVEF <math>&lt;45\%</math> or NSVT, an ICD is reasonable.</b>	161
<b>IIa</b>	<b>B-NR</b>	<b>In individuals with lamin A/C ACM and two or more of the following: LVEF <math>&lt;45\%</math>, NSVT, male sex, an ICD is reasonable.</b>	156

In a cohort of 403 patients from the Netherlands with the founder R14del variant in *PLN*, independent variables associated with malignant arrhythmias included LVEF  $<45\%$ , sustained VT or NSVT.<sup>161</sup> Other variables were associated with malignant arrhythmias, but none of these remained significant after multivariate analysis. Although sustained VT was not studied in the lamin A/C cohorts, a finding of NSVT on Holter monitoring was a significant predictor for spontaneous VT/VF in a cohort of 269 patients.<sup>156</sup>

In patients with lamin A/C, several clinical variables are associated with the risk of spontaneous VT/VF or ICD-treated VT/VF. In a cohort of 269 patients from a European registry, NSVT on Holter monitoring, LVEF  $<45\%$ , and male sex were associated with VT/VF, but only if a patient had 2 or more of these factors.<sup>156</sup> In an international registry of 122 patients, male sex, LVEF  $\leq 50\%$  at the first clinical contact, and nonmissense variants were independent predictors of arrhythmias.<sup>32</sup> In this study, the risk of arrhythmia increased exponentially as the number of these predictors increased. During the 7-year follow-up, the incidence of sustained VT/VF was 9% with 1 of these risk factors, increasing to 28% with 2, 47% with 3, and 69% with 4 risk factors.



COR	LOE	Recommendations	References
IIa	C-LD	<b>In individuals with <i>FLNC</i> ACM and an LVEF &lt;45%, an ICD is reasonable.</b>	34

Variants in *FLNC* are associated with several skeletal and cardiac myopathies. Variants in *FLNC* are associated with several skeletal and cardiac myopathies. Pathogenic variants in *FLNC* were recently recognized to cause ACM, resulting, in part, from the identification of truncation variants in 28 unrelated cardiomyopathy patients referred to a gene testing laboratory in Spain.<sup>34</sup> Familial evaluation led to the identification of 54 individuals with *FLNC* variants. SCD and arrhythmias treated by an ICD were frequent. In the 12 patients with SCD, the mean LVEF was 39.6% + 12%.

COR	LOE	Recommendations	References
IIa	C-LD	<b>In individuals with lamin A/C ACM and an indication for pacing, an ICD with pacing capabilities is reasonable.</b>	149,170,189

In some cohort studies,<sup>149,170,189</sup> AV block was a univariate predictor for VT or VF, thereby justifying consideration of an ICD if pacing is needed.

### 3.11. Management of ventricular arrhythmia and dysfunction

#### 3.11.1. Medications including angiotensin-converting enzyme inhibitors, beta-blockers, and antiarrhythmic drugs

See Evidence Table: Medical Therapy for Ventricular Arrhythmia and Dysfunction. Recommendation flow diagrams are shown in Figure 13 and Figure 14.

The aim of medical therapy in ACM is to control the ventricular dimensions and function, manage the congestive symptoms, and prevent and treat the arrhythmia. The management of HF in ACM involves two different aspects of myocardial dysfunction: LV failure and RV failure.

##### 3.11.1.1. Medical therapies for left ventricular failure

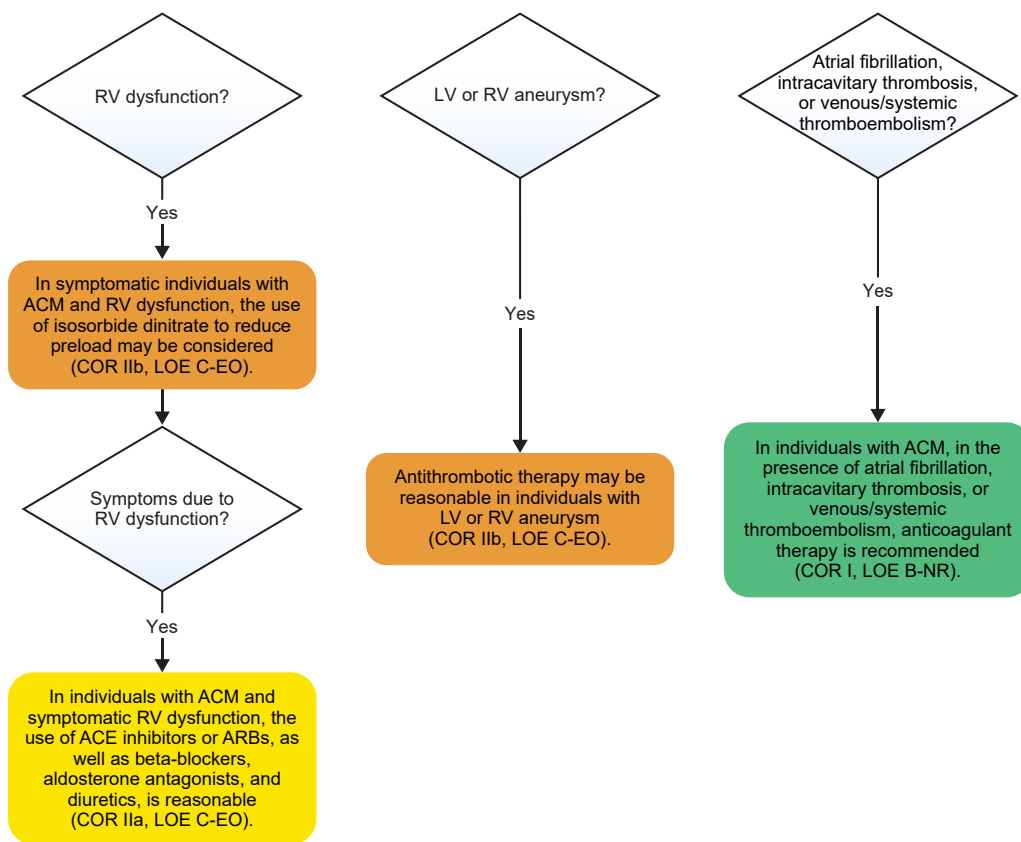
ALVC that phenotypically overlaps with classic DCM predominantly affects the LV. In this case, the treatment of symptomatic and asymptomatic HF with reduced ejection fraction (HFrEF) in the LV follows the current 2013 (updated in 2016) AHA/ACC<sup>7,8</sup> and ESC guidelines.<sup>9</sup> Guideline-directed therapies include angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), beta-blockers, aldosterone antagonists, and, in

selected cases, vasodilators (hydralazine and isosorbide dinitrate).<sup>8,9,192</sup> The 2016 recommendations of the AHA/ACC<sup>7</sup> and ESC guidelines<sup>9</sup> include new drugs: the angiotensin receptor-neprilysin inhibitor (valsartan/sacubitril<sup>193</sup>) and the sinoatrial modulator, ivabradine.<sup>193,194</sup> The therapy for congestive symptoms includes loop diuretics and volume control, with recommendations for a low-sodium diet.<sup>8,9</sup> The benefit of digitalis for symptoms in patients with sinus rhythm has been debated; however, a recent retrospective analysis of the randomized Digitalis Investigation Group trial suggested that patients with LVEF <40% (HFrEF) and patients with LVEF 40%–50% (HF with mid-range ejection fraction, HFmrEF) had a benefit in terms of mortality and hospitalization (HFmrEF) or hospitalization only (HFrEF) from digitalis therapy.<sup>195</sup> Additionally, patients with reduced LVEF may benefit from cardiac resynchronization therapy,<sup>196</sup> LV-assist devices, and heart transplantation.<sup>8,9</sup> In a systematic review of 4 studies evaluating the use of digitalis for RV failure, which were limited to patients with cor pulmonale, there was no evidence of benefit in terms of improvement in RVEF, exercise capacity, or NYHA class.

##### 3.11.1.2. Medical therapies for right ventricular failure

COR	LOE	Recommendations	References
IIa	C-EO	<b>In individuals with ACM and symptomatic RV dysfunction, the use of ACE inhibitors or ARBs, as well as beta-blockers, aldosterone antagonists, and diuretics, is reasonable. In symptomatic individuals with ACM and RV dysfunction, the use of isosorbide dinitrate to reduce preload may be considered.</b>	
IIb	C-EO		

The therapy to reverse ventricular remodeling in RV failure (typical of ARVC) is less established due to the lack of trials specifically addressing patients with ARVC. In an ARVC model of plakoglobin knockdown in mice, the preload-reducing treatment using a combination of diuretics and isosorbide dinitrate prevented the development of ARVC induced by endurance exercise training.<sup>197</sup> These data suggest a potential benefit of preload-reducing therapy in early stages of RV remodeling.



**Figure 13** Recommendations for ventricular dysfunction and antithrombotic medical therapy in individuals with arrhythmogenic cardiomyopathy (ACM). ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; COR = Class of Recommendation; LOE = Level of Evidence; LV = left ventricular; RV = right ventricular. Colors correspond to COR in Figure 1.

3.11.1.3. Antithrombotic therapy in arrhythmogenic cardiomyopathy

COR	LOE	Recommendations	References
I	B-NR	<b>In individuals with ACM, in the presence of atrial fibrillation, intracavitary thrombosis, or venous/systemic thromboembolism, anticoagulant therapy is recommended.</b>	198

Patients with ARVC can develop “atrial disease” and predisposition to atrial tachyarrhythmias. In the absence of atrial fibrillation, however, there is no clear evidence of a benefit from anticoagulation compared with placebo or aspirin in HF.<sup>199,200</sup> Specifically in the ARVC population, a study of 126 patients with ARVC found a relatively lower risk of thromboembolism in ARVC compared with LV HF; however, patients with severely dilated and hypokinetic RVs with slow blood flow and spontaneous echocardiographic contrast were at higher risk.<sup>198</sup> Overall, anticoagulation is appropriate for the ACM population (ALVC and ARVC) to reduce the stroke risk in patients with atrial fibrillation in accordance with the current ACC/AHA and ESC guidelines for the management of atrial fibrillation,<sup>201,202</sup> intracavitary thrombosis, and venous or systemic thromboembolism. In the absence of these factors, however, there is no evidence of a benefit from anticoagulation compared with placebo or aspirin.

COR	LOE	Recommendations	References
IIb	C-EO	<b>Antithrombotic therapy may be reasonable in individuals with LV or RV aneurysm.</b>	

ACM may carry an increased risk of thromboembolic events. In ALVC risk is increased by intraventricular thrombus formation in severe LV dysfunction, and in ARVC by not only RV dysfunction but also localized aneurysms and sacculations. Furthermore, some patients with ARVC can develop “atrial disease” and predisposition to atrial tachyarrhythmias. There are no data to indicate antithrombotic therapy in isolated RV dysfunction.

## 3.11.1.4. Arrhythmia management

COR	LOE	Recommendations	References
<b>I</b>	<b>C-LD</b>	<b>Beta-blocker therapy is recommended in individuals with ACM with inappropriate ICD interventions resulting from sinus tachycardia, supraventricular tachycardia, or atrial fibrillation/flutter with high ventricular rate.</b>	<a href="#">203</a>

Beta-blocker therapy may prevent the occurrence of supraventricular arrhythmias within the programmed VT detection zone. Inappropriate ICD shocks, which are typically due to supraventricular arrhythmias, are to be avoided, and studies of HF patients have demonstrated improved outcomes when the number of inappropriate shocks is reduced.<sup>204–206</sup> There are no randomized studies on specific beta-blockers in ACM. In the general population with HF, a nonrandomized post hoc substudy of the Multicenter Automatic Defibrillator Implantation with Cardiac Resynchronization Therapy (MADIT-CRT) trial showed the effectiveness of beta-blockers (carvedilol in particular) in reducing the number of inappropriate ICD therapies for patients who received an ICD with or without biventricular pacing.<sup>205</sup>

COR	LOE	Recommendations	References
<b>IIa</b>	<b>C-EO</b>	<b>Beta-blocker therapy is reasonable in individuals with ACM who do not have an ICD.</b>	

In patients clinically affected by ACM, beta-blockers can prevent adrenergic arrhythmias, exercise-induced arrhythmias, and ventricular remodeling, although there are no controlled clinical trials to unequivocally demonstrate the drugs' benefit. In a cohort of well-characterized individuals with ARVC, beta-blockers were not significantly effective.<sup>183</sup> In unaffected carriers (genotype-positive or phenotype-negative), the lack of information currently does not support long-term beta-blocker therapy.

COR	LOE	Recommendations	References
<b>IIb</b>	<b>B-NR</b> <b>C-LD</b>	<b>Amiodarone (LOE B-NR) and sotalol (LOE C-LD) may be reasonable in individuals with ACM for control of arrhythmic symptoms or to reduce ICD shocks.</b>	<a href="#">183,207,208</a>

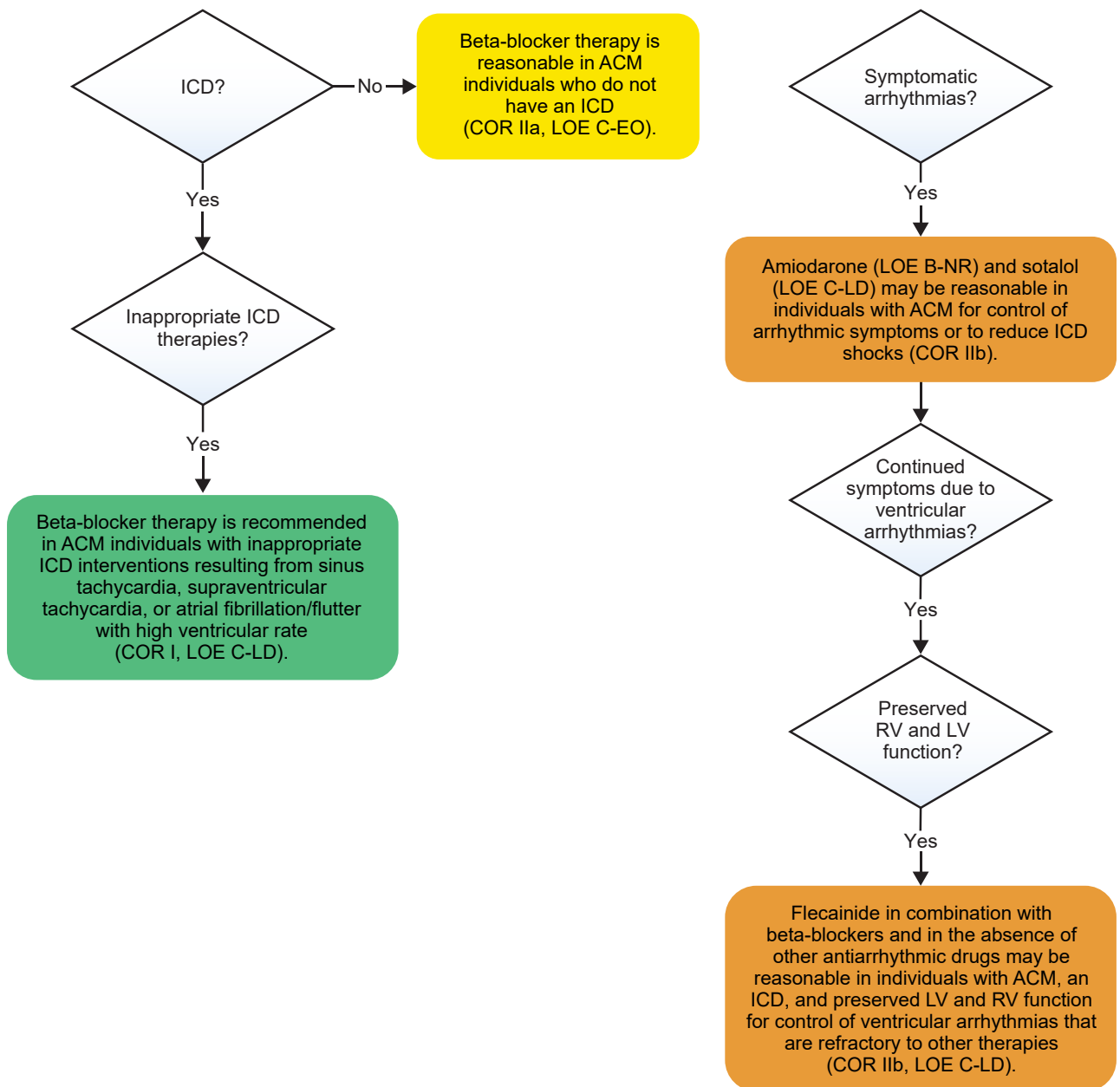
In patients with ventricular arrhythmias, antiarrhythmic therapy can be used to control symptoms. In a study of 95 patients with ARVC, the most effective drug appeared to be amiodarone,<sup>207</sup> whereas there was no significant evidence for the efficacy of sotalol and beta-blockers. In a more recent series of 301 patients with ARVC, however, neither beta-blocker, amiodarone, nor sotalol reduced life-threatening arrhythmic events.<sup>183</sup>

Given that patients with ARVC are predominantly younger than conventional HF patients, sotalol therapy before amiodarone in the earlier phases of the disease can be justified to avoid long-term use and prevent the adverse extracardiac effects of amiodarone, although there are no robust data to support this approach in this ARVC patient population.

The Optimal Pharmacological Therapy in Implantable Cardioverter Defibrillator Patients (OPTIC) trial randomized 412 patients with an ICD (but not specifically ACM) and inducible or spontaneous VT or VF to treatment with amiodarone with a beta-blocker, sotalol alone, or a beta-blocker alone.<sup>208</sup> Sotalol showed a trend to reduce all-cause ICD shocks at 1 year from 38.5% to 24.3% (HR: 0.61;  $P = .055$ ). Patients treated with sotalol should have a normal or near-normal QT interval at baseline, and normal or near-normal renal function. Compared with beta-blocker therapy alone, amiodarone reduced the number of ICD shocks (HR 0.27;  $P < .001$ ),<sup>208</sup> but this came at the cost of more adverse effects.<sup>43</sup>

COR	LOE	Recommendations	References
<b>IIb</b>	<b>C-LD</b>	<b>Flecainide in combination with beta-blockers and in the absence of other antiarrhythmic drugs may be reasonable in individuals with ACM, an ICD, and preserved LV and RV function for control of ventricular arrhythmias that are refractory to other therapies.</b>	<a href="#">209</a>

In a small series of patients, the addition of flecainide in combination with sotalol or metoprolol was found to be effective for controlling ventricular arrhythmias in patients with an ICD and ARVC refractory to single-agent therapy and/or catheter ablation.<sup>209</sup> Data from patients with CPVT, including a recent randomized trial,<sup>210</sup> also suggest the efficacy of flecainide in these patients, which could be extrapolated to the population with ARVC.<sup>211</sup> Overall, these findings suggest the potential benefit of flecainide in combination with beta-blockers for patients with refractory ventricular arrhythmias.



**Figure 14** Medical therapy recommendations for arrhythmias. ACM = arrhythmogenic cardiomyopathy; COR = Class of Recommendation; ICD = implantable cardioverter defibrillator; LOE = Level of Evidence; LV = left ventricular; RV = right ventricular. Colors correspond to COR in Figure 1.

3.11.2. Role of catheter ablation

See Evidence Table: Catheter Ablation. A recommendation flow diagram is shown in Figure 15.

COR	LOE	Recommendations	References
IIa	B-NR	<b>In individuals with ACM and recurrent sustained monomorphic VT who have failed or are intolerant of amiodarone, catheter ablation is reasonable for reducing recurrent VT and ICD shocks.</b>	212-222

Catheter ablation is a well-studied therapy for almost all forms of cardiomyopathy, especially for patients with ischemic scars and those with idiopathic dilated cardiomyopathies.<sup>223-225</sup> Catheter ablation is recognized as a central treatment option for patients with ventricular arrhythmias who have received therapies from their ICDs, and in the context of failure or intolerance of antiarrhythmic drugs.<sup>213,214</sup> For ARVC, evidence from single-center and multicenter cohorts has demonstrated the effectiveness of ablation in reducing the incidence of recurrent VT events and ICD shocks.<sup>218-222</sup>

(Continued)

(Continued)

Although the outcomes are dictated more by the underlying arrhythmogenic substrate and the disease process, there are nevertheless similarities in the pathophysiology and strategies for catheter ablation across all forms of structural heart disease. Compared with patients with healthy hearts, patients with structural heart disease (including those with ischemic heart disease, DCMs, and all forms of ACM) all retain a diseased ventricular myocardium and various degrees of fibrosis or scars. These are fundamental substrates for reentrant ventricular arrhythmia and can therefore be targeted if the patient presents with monomorphic VT.<sup>226–229</sup> Ablation for all forms of structural heart disease is aimed at removing or ameliorating this arrhythmogenic element, and extrapolation is therefore employed in this section, given the limited data for the rare or less-defined cardiomyopathies. Catheter ablation of VT associated with LMNA cardiomyopathy is associated with poor outcomes, including a high rate of arrhythmia recurrence, progression to end-stage HF, and high mortality.<sup>230</sup> There are only isolated case reports for catheter ablation of VT in patients with LVNC,<sup>231,232</sup> cardiac amyloidosis,<sup>233,234</sup> and Fabry disease<sup>235</sup>; the bulk of the data concern procedural approaches and outcomes for patients with arrhythmogenic RV dysplasia or cardiomyopathy.<sup>216,218–222,236,237</sup>

COR	LOE	Recommendations	References
IIa	B-NR	<b>In individuals with ACM and recurrent symptomatic sustained VT in whom antiarrhythmic medications are ineffective or not tolerated, catheter ablation with availability of a combined endocardial/epicardial approach is reasonable.</b>	216,218–222
	C-EO	<b>In symptomatic individuals with ACM and a high burden of ventricular ectopy or nonsustained VT in whom beta-blockers and/or antiarrhythmic medications are ineffective or not tolerated, catheter ablation with availability of a combined endocardial/epicardial approach is reasonable.</b>	

Unlike many ischemic cardiomyopathies in which the diseased substrate is easily accessed transvenously, arrhythmogenic RV dysplasia and cardiomyopathy frequently require an epicardial approach, which is directly related to the location of the diseased tissue.<sup>216,218–222,236,237</sup> This particular approach has been relatively well-studied in terms of outcomes and technical approach. Freedom from ventricular arrhythmias and ICD therapies is definitively improved with combined endocardial and epicardial ablation. Interrupting the diseased substrate and targeting the clinical VT have provided higher long-term success rates of approximately 60%–80%. Therefore, a combined endocardial and epicardial approach is helpful when targeting symptomatic ventricular arrhythmias. These recommendations do not address the separate question of how to approach a patient who has already failed an endocardial approach or whether an epicardial approach should be employed as the first line.

COR	LOE	Recommendations	References
IIb	C-LD	<b>Individuals with ACM and recurrent symptomatic sustained VT in whom medical therapy has not failed may be considered for catheter ablation.</b>	216,218,220

In some catheter ablation studies of patients with ACM, antiarrhythmic drug therapy was not mandated for inclusion. However, the number of such patients included in these studies was limited. This recommendation addresses patients with recurrent symptomatic sustained VT who desire ablation either as first-line treatment or to reduce or avoid medical therapy that has been effective.

Current technology and techniques suggest that electroanatomical mapping supports better outcomes, which is routinely employed at all major centers. These methods are routinely employed to more accurately define scars and disease. Ablations for the more unusual cardiomyopathies are performed at high-volume referral centers, which are more accustomed to the idiosyncrasies of each cardiomyopathy subtype. These centers provide highly trained operating room staff, anesthesiologists, and surgical backup.

Catheter ablation for patients with ARVC should not be considered curative for the underlying arrhythmogenic substrate and is ultimately aimed at improving quality of life by limiting symptomatic ectopy, sustained arrhythmia, and especially ICD therapies. There are insufficient data showing disease progression is affected, sudden death is prevented, or mortality is reduced.

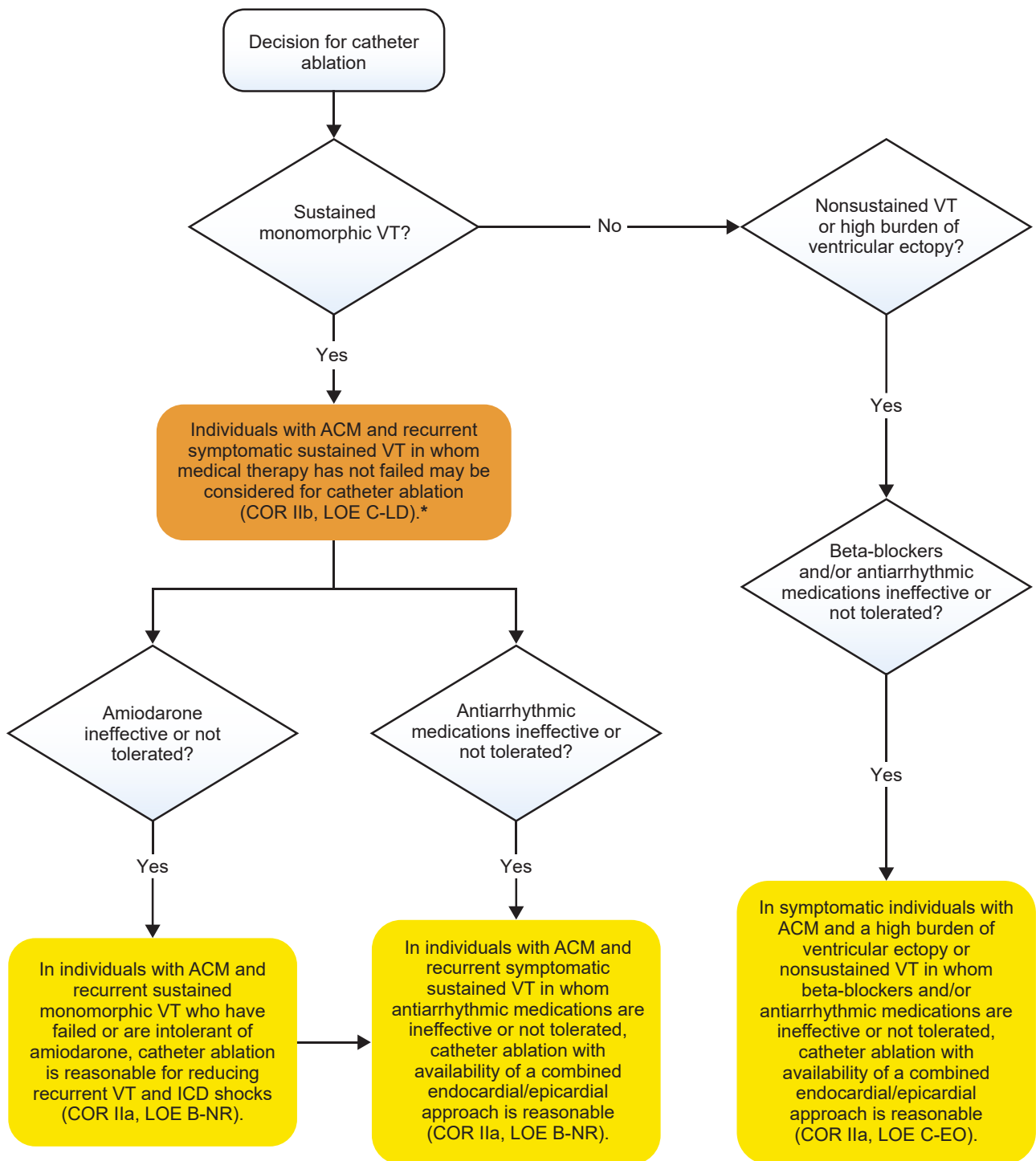
### 3.12. Prevention of disease progression

See Evidence Table: Exercise Restriction. A recommendation flow diagram is shown in Figure 16.

Clinicians have long recognized that patients with ARVC were disproportionately athletes<sup>238</sup> and that athletic patients with ARVC have a high risk of SCD.<sup>239</sup> A seminal review of autopsies in Italy showed that participation in competitive athletics resulted in a more than 5-fold increase in SCD risk among adolescents and young adults with ARVC<sup>240</sup> and that implementing a preparticipation screening program resulted in a sharp decline in deaths.<sup>241</sup>

The discovery that pathogenic variants in genes encoding the cardiac desmosome were present in up to 60% of patients with ARVC provided insight into the connection between exercise and ARVC.<sup>145</sup> Murine ARVC models with abnormal expression of desmosomal proteins have consistently shown exercise-induced or exercise-exacerbated cardiovascular phenotypes.<sup>242–246</sup> Defining the molecular mechanisms of this process is an active area of research.

These discoveries also prompted research to more precisely define the role of exercise in penetrance, arrhythmic risk, and structural progression in patients with ARVC and their at-risk relatives. These studies (reviewed below) make a compelling case

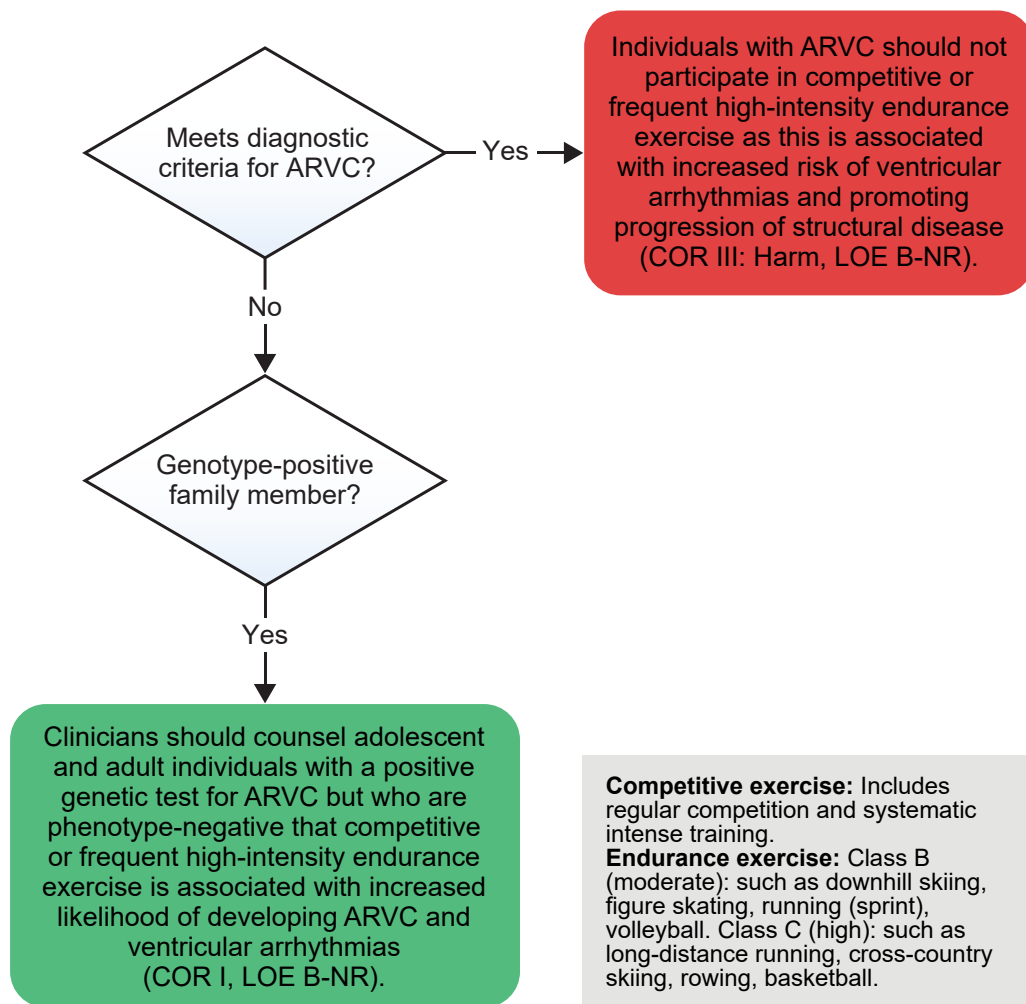


\*This recommendation does not exclude the choice to continue medical therapy that has not failed and not proceed with ablation

**Figure 15** Catheter ablation recommendations for individuals with arrhythmogenic cardiomyopathy (ACM). COR = Class of Recommendation; ICD = implantable cardioverter defibrillator; LOE = Level of Evidence; VT = ventricular tachycardia. Colors correspond to COR in Figure 1.

that (1) there is a dose-dependent relationship between exercise exposure and ARVC onset (penetrance) and severity; and (2) frequent high-intensity or competitive exercise in patients with established ARVC is associated with worse clinical outcomes.

**3.12.1. Clinical exercise questions to direct a literature search**  
In this section, we used the PICO format to construct questions to direct a literature search. The following questions were analyzed:



**Figure 16** Exercise recommendations for individuals with arrhythmogenic right ventricular cardiomyopathy (ARVC). COR = Class of Recommendation; LOE = Level of Evidence. Colors correspond to COR in Figure 1.

1. Should a family member who is mutation-positive but phenotype-negative be restricted from strenuous exercise to prevent ARVC disease expression?
2. Should patients who meet Task Force Criteria for the diagnosis of ARVC, regardless of symptoms or disease severity, be restricted from strenuous exercise, compared to no restriction, to prevent VT or VF?
3. Should patients who meet Task Force Criteria for the diagnosis of ARVC, regardless of symptoms or disease severity, be restricted from strenuous exercise, compared to no restriction, to prevent progression of RV or LV dysfunction?

### 3.12.2. Exercise definitions

To best translate the results of these studies to clinical practice, it is important to consider how each study collects exercise history and defines an individual as an athlete. Physical activity has 4 broad dimensions: (1) mode or type of activity, (2) frequency, (3) duration, and (4) intensity.<sup>247</sup> Activity can be considered recreational or competitive and categorized based on peak static and dynamic demand. Here, we define “endurance” exercise as that with a moderate or high dynamic demand as per the

AHA/ACC Scientific Statement for Eligibility and Disqualification Recommendations for Competitive Athletes with Cardiovascular Abnormalities<sup>248</sup> (class C and B activities). Similarly, we define “competitive exercise” as “participation in an organized team or individual sport that requires regular competition against others as a central component, places a high premium on excellence and achievement and requires some form of systematic (and usually intense) training,” consistent with these guidelines.<sup>249</sup>

Intensity, duration, and frequency of aerobic physical activity can be integrated into one measure (metabolic equivalent [MET]-minutes/week) for an exercise “dose.” For instance, the AHA minimum recommended exercise for healthy adults is 450–750 MET-minutes weekly.<sup>250</sup> A MET is the ratio of the work metabolic rate to the resting metabolic rate. Vigorous-intensity activities are generally considered those requiring  $\geq 6$  METs.<sup>251</sup> The 2011 Adult Compendium of Physical Activities provides a comprehensive listing of the METs associated with a variety of physical activities (<https://sites.google.com/site/compendiumofphysicalactivities/>).<sup>252</sup> Figure 17 includes examples of METs associated with common types of endurance exercise.

Frequency	Intensity	METs	Examples of METs associated with endurance exercise
Never/ Rare	High	16	Competitive cycling
		15	Cross-country ski racing (>8.0 mph)
		12	Canoeing, rowing, crew in competition
		10	Soccer, competitive
		9.8	Running—6 mph (10 minutes/mile)
		8	Basketball game
		7	Racquetball
		5.8	Swimming laps, freestyle—light-moderate effort
		5.3	Downhill skiing—moderate effort
		5	Walking for exercise—4 mph (very brisk pace, level, firm surface)
Regular	Low	4.8	Golf
		3.5	Walking for pleasure or transportation
		3.3	Sailing (boat and board sailing, windsurfing, ice sailing)
		3	Canoeing/rowing for pleasure
		2.5	Yoga

**Figure 17** Metabolic equivalents (METs) associated with common types of endurance exercise (<https://sites.google.com/site/compendiumofphysicalactivities/>).<sup>247,252</sup> Inverse association between intensity of exercise (METs) and recommended frequency of participation among patients with arrhythmogenic right ventricular cardiomyopathy (ARVC). Aiding patients and at-risk family members in making choices about participation in various types of exercise involves ongoing discussion and shared decision making. Based on data suggesting that higher exercise intensity and doses (intensity\*duration) are associated with poorer outcomes,<sup>254,255,258,259</sup> vigorous-intensity activities (red/orange) should be performed rarely if at all, and lower-intensity activities (green) more regularly. This figure is provided to aid the clinician in understanding METs associated with a variety of common activities<sup>252</sup> and to aid in discussions with patients and families.

### 3.12.3. Exercise increases age-related penetrance among genotype-positive relatives

Evidence from several retrospective studies suggests there is a dose-dependent relationship between endurance exercise and the likelihood of developing ARVC. A study of 87 carriers of heterozygous desmosomal variants showed that participation in vigorous endurance athletics and a longer duration of annual exercise were associated with an increased likelihood of ARVC diagnosis and of developing sustained ventricular arrhythmias.<sup>253</sup> Endurance athletes were defined as participants in a sport with a high dynamic demand<sup>248</sup> for at least 50 hours per year at vigorous intensity. A separate analysis using the same definitions<sup>171</sup> further showed that patients with ARVC with adolescent onset were significantly more likely to have been endurance athletes during their youth than were patients with ARVC diagnosed as adults. Finally, a third study confirmed that in 10 families with a segregating *PKP2* variant, family members who developed ARVC were more likely to be athletes and to have engaged in a significantly higher exercise dose across their lifespan than family members without disease.<sup>254</sup>

Consistent with this, Saberniak et al<sup>255</sup> showed that athletes (1440 MET-minutes/week for a minimum of 6 years) were more likely to be diagnosed with ARVC, and the age of starting athletic training was correlated with age of ICD implantation, suggesting a temporal relationship between the timing of exercise exposure and disease onset. This study also illustrated a linear relationship between the amount of physical activity

and the extent of RV and LV dysfunction in patients and at-risk family members. Among asymptomatic family members, athletes had worse LV function and more RV abnormalities. It is important to recognize that most of these data are from carriers of *PKP2* variants, and the association between exercise and penetrance in carriers of other desmosomal and nondesmosomal ARVC-related variants awaits confirmation.

Nonetheless, taken together, these studies establish that the likelihood that genotype-positive relatives of patients with ARVC will develop disease is strongly associated with frequent endurance exercise. Thus, presymptomatic genetic testing not only facilitates early diagnosis but also provides the opportunity to decrease the risk of developing ARVC through lifestyle changes. Clinicians should counsel these patients that competitive or frequent high-intensity endurance exercise is associated with an increased likelihood of developing ARVC.

#### 3.12.3.1. Exercise for carriers of pathogenic variants detected incidentally

It is important to recognize that these data are from genotype-positive patients who are also relatives of patients with ARVC. ARVC-associated pathogenic variants are increasingly identified through population-based sequencing studies and direct-to-consumer genetic testing.<sup>11</sup> The desmosomal genes are also included in the list of 59 genes recommended by the ACMG for return when discovered as secondary findings.<sup>162</sup> Research suggests that the penetrance of variants



detected in this setting is lower than for family members identified through cascade testing.<sup>163</sup> The benefit of limiting frequent high-intensity or competitive endurance exercise for these patients may thus be lower but requires further study.

3.12.3.2. *Exercise and relatives of “gene-elusive” patients with arrhythmogenic right ventricular cardiomyopathy*

Evidence is emerging that there is a cohort of athletic patients with ARVC without pathogenic variants who may have a largely exercise-induced form of disease. These patients are characterized by very high levels of athletic activity, no identifiable pathogenic desmosomal variant, and an absence of family history.<sup>256,257</sup> Unaffected family members of such patients with a normal initial evaluation may have a considerably lower likelihood of developing ARVC. These patients should undergo cardiac evaluation every 1–3 years as described in Section 3.9 Cascade Family Screening. At present, however, there is no strong evidence to recommend limiting exercise.

3.12.3.3. *Exercise increases arrhythmic risk and structural dysfunction in patients with arrhythmogenic right ventricular cardiomyopathy*

In contrast to the still-limited data available to inform recommendations for patients with a positive genetic test for ARVC but who are phenotype-negative (genotype-positive, phenotype-negative), a growing group of studies have consistently shown that competitive or frequent high-intensity endurance exercise is associated with a higher risk of ventricular arrhythmias regardless of genotype.<sup>183,253,255,256,258,259</sup> Although the definitions of athletic activity vary across these studies, the outcomes are the same, with participation in high-intensity, strenuous, competitive, high-duration exercise associated with poorer survival free from sustained ventricular arrhythmias. This result is not surprising, given that data from autopsy studies have shown that ARVC-related SCD often occurs with vigorous exercise.<sup>260,261</sup> Recently, Lie et al<sup>259</sup> further established that while high-intensity and long-duration exercise were associated with ventricular arrhythmias, intensity remained an independent predictor after adjusting for duration, highlighting the importance of limiting high-intensity exercise.

Several studies have suggested that the risk of arrhythmias during follow-up can be modified by reducing exercise. Desmosomal variant carriers who reduced their exercise after

the clinical presentation had a lower incidence of ventricular arrhythmia compared with patients who continued to participate in intense and/or long-duration exercise.<sup>253</sup> This finding was replicated in a study of 108 probands from the North American ARVC Registry that showed patients who continued self-defined competitive exercise had a significantly worse arrhythmic course.<sup>258</sup> In contrast, there were no significant differences in the risk of ventricular arrhythmias or death between the inactive patients and the recreational athletes, although recreational athletes had worse LV function. Finally, Wang et al<sup>262</sup> showed that, among 129 patients with ARVC with ICDs, patients who reduced their exercise dose (MET-hours/year) the most had the best survival from ICD therapy in follow-up. These data suggest that gene-elusive patients and those who have had an ICD implanted for primary prevention may benefit the most from reducing their exercise dose.

The extent of both RV and LV structural dysfunction is also correlated with exercise history for patients with ARVC. This finding was first observed by Sen-Chowdhry et al,<sup>80</sup> who found that, of 116 patients with ARVC, the 11 patients who participated in long-term endurance training had more severe RV dysfunction. Sawant et al showed that among nondesmosomal “gene-elusive” patients with ARVC, those who had performed a higher average MET-hours-year of exercise were most likely to have major RV structural abnormalities.<sup>256</sup> Saberniak et al performed an extensive analysis and demonstrated that RV and LV function was significantly reduced in athletes and that exercise was correlated with the extent of structural dysfunction in a dose-dependent fashion.<sup>255</sup> Although no study has prospectively assessed the effect of exercise reduction on structural progression, athletic activity is associated with poor clinical outcomes. Saberniak et al<sup>255</sup> showed that only athletes progressed to transplantation, while James et al<sup>253</sup> showed that only athletes developed class C HF.

3.12.4. *Exercise and other arrhythmogenic cardiomyopathies*

In contrast to ARVC, there are limited genotype-specific data from which to make exercise recommendations for other ACMs. Similar to desmosomal and “gene-elusive” ARVC patients, ventricular arrhythmias occur disproportionately during exercise in patients with the R14del *PLN* variant.<sup>161</sup> Preliminary studies suggest, however, that a history of athletics is not associated with disease penetrance in these patients.

COR	LOE	Recommendations	References
I	B-NR	<b>Clinicians should counsel adolescent and adult individuals with a positive genetic test for ARVC but who are phenotype-negative that competitive or frequent high-intensity endurance exercise is associated with increased likelihood of developing ARVC and ventricular arrhythmias.</b>	171,253–255

Competitive or frequent high-intensity endurance exercise increases the risk of developing RV and LV dysfunction. Athletic activity prior to and after disease presentation also increases the risk of ventricular arrhythmias and is associated with poorer survival from sustained ventricular arrhythmias.<sup>171,253–255</sup> A positive genetic test indicates a pathogenic or likely pathogenic variant in an ARVC-associated gene per the ACMG guidelines for variant adjudication.<sup>95</sup>

COR	LOE	Recommendations	References
<b>III: Harm</b>	<b>B-NR</b>	<b>Individuals with ARVC should not participate in competitive or frequent high-intensity endurance exercise as this is associated with increased risk of ventricular arrhythmias and promoting progression of structural disease.</b>	80,171,183,253–255,258

Competitive or frequent high-intensity endurance exercise is related to the extent of RV and LV dysfunction in patients with ARVC. Additionally, such exercise is associated with poorer outcomes for ventricular arrhythmias, whereas reducing exercise has a more favorable arrhythmic prognosis. Aiding patients and at-risk family members in making choices about participation in various types of exercise involves ongoing discussion and shared decision making.

**Competitive exercise** includes participation in “an organized team or individual sport that requires regular competition against others as a central component, places a high premium on excellence and achievement, and requires some form of systematic (and usually intense) training” as defined by the AHA/ACC Scientific Statement for Eligibility and Disqualification Recommendations for Competitive Athletes with Cardiovascular Abnormalities.<sup>249</sup>

**Endurance exercise** includes class C and B sports in these guidelines.<sup>248</sup> Data on the effect of static exercise (Class A) on outcomes are largely absent from the literature. **Intensity** is typically measured in METs.<sup>252</sup>

For the basic science details of the mechanisms responsible for the forms of ACM, please see Section 4 Disease Mechanisms.

## Section 4 Disease mechanisms

An overview of some of the disease mechanisms for ACM is shown in Figure 18.

### 4.1. Desmosomal defects

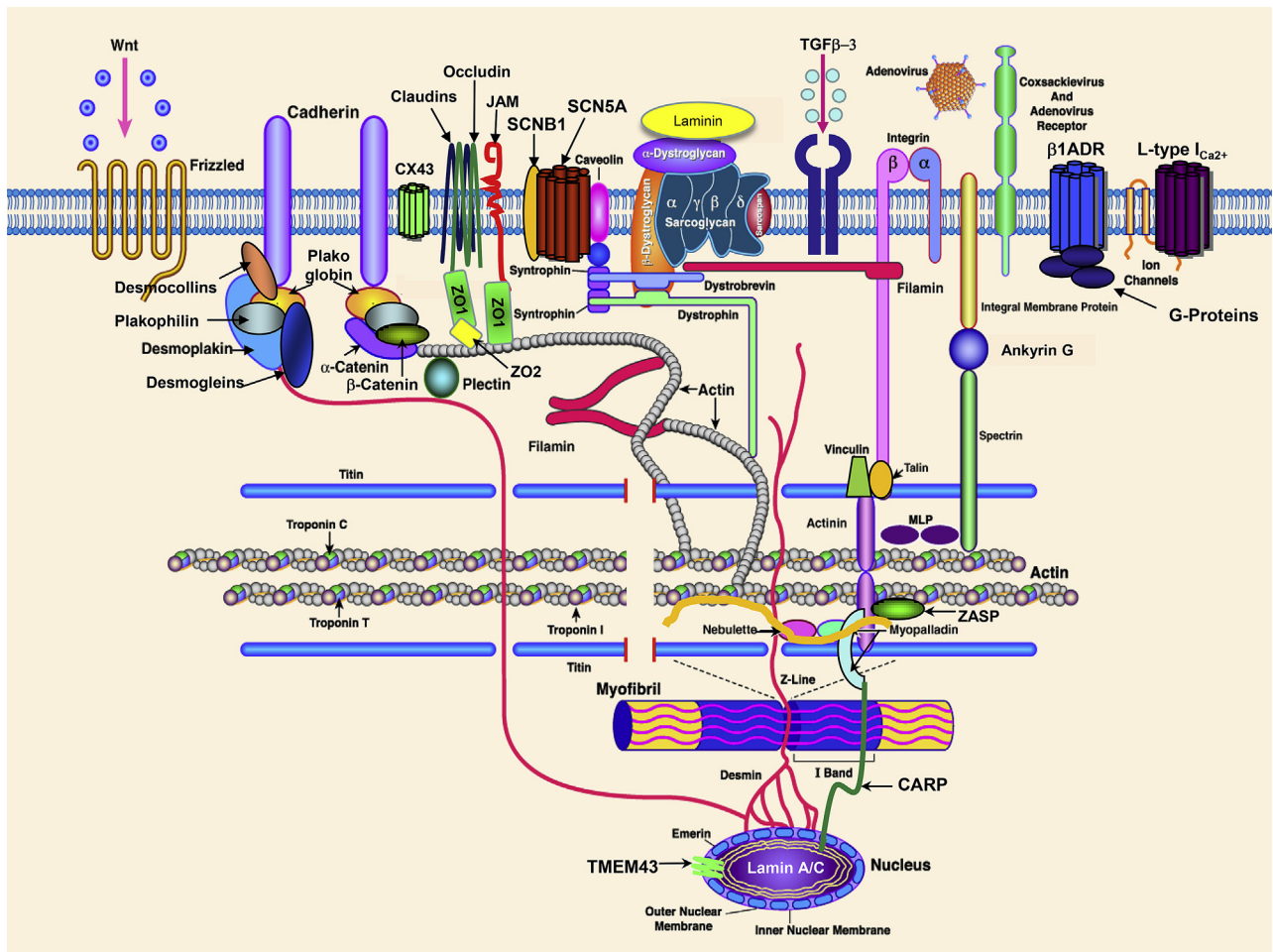
The cardiac ID is a highly organized structure that connects adjacent cardiomyocytes and is classically comprised of three main structures: (1) gap junctions (GJs), which metabolically and electrically connect the cytoplasm of adjacent cardiomyocytes; (2) adherens junctions (AJs), which connect the actin cytoskeleton of adjacent cells; and (3) desmosomes, which function as cell anchors and connect intermediate filaments (IFs). In addition, ion channels reside in the ID. Pathologic genetic variants in ID proteins have been associated with cardiac arrhythmias, such as BrS, ARVC, and other genetically determined ACMs.<sup>263,264</sup> However, rather than being independent, all ID components work closely together by partnering with multifunctional proteins such as ZO-1, ankyrin G, and  $\beta$ -catenin, allowing the ID to integrate mechanical and electrical functions. GJs form a plaque surrounded by the perinexus in which free connexons reside; the connexome integrates sodium ( $\text{Na}_v$ ) channels, the desmosome, and GJs; and the area composita hosts AJs and desmosomes, also integrated as adhering junctions. Furthermore, the transitional junction connects sarcomeres to the plasma membrane. The ID ensures rapid propagation of the electrical signal that initiates contraction throughout the heart and allows the cardiomyocytes to withstand the strong mechanical forces imposed by the beating of

the heart. AJs, desmosomes, GJs, and ion channels form a functional unit as the area composita. Furthermore, GJs and ion channels likely create and propagate action potentials (APs) together. Some structural components of cell–cell junctions can also interact with other ID proteins or function in signaling pathways, such as Cx43 and  $\beta$ -catenin. Protein deficiencies can ultimately lead not only to mechanical dysfunction (eg, AJ dysfunction) but also to arrhythmias, often via GJ remodeling, thereby illustrating the interdependency of ID components and the coupling of mechanical and electrical elements.

The lateral membrane (LM) of cardiomyocytes has a different makeup compared to the ID, hosting, among others, costameres and focal adhesions and linking sarcomeres to the extracellular matrix. The ID and LM have several proteins in common, such as vinculin and  $\alpha$ -actinin, and ion channels.

The AJ is the primary anchor for myofibrils and connects actin filaments from adjacent cells, which allows the cell to retain its shape under mechanical stress. Furthermore, the AJ transduces signals concerning the actin cytoskeleton and senses mechanical forces on the cell. The transmembrane protein N-cadherin is the main constituent of AJs and homodimerizes with N-cadherins from adjacent cells in the extracellular space, acting as an intercellular zipper. This action provides tissue specificity during development, allowing cells to interact only with cells expressing the same cadherin. Calcium ions ensure the rod shape of N-cadherin, the intracellular domain which primarily binds  $\beta$ -catenin. N-cadherin also possesses regulatory functions including a role in mechanosensing.  $\beta$ -catenin directly interacts with the C-terminal cytoplasmic domain of N-cadherin. By associating with  $\alpha$ -catenin and vinculin,  $\beta$ -catenin connects AJs to the actin cytoskeleton.

$\beta$ -catenin also plays a central role in cadherin-mediated signaling and can activate the canonical Wnt signaling pathway.  $\beta$ -catenin translocates to the nucleus when Wnt binds its Frizzled receptor, to initiate transcription of transcription factors of the T-cell factor/lymphoid enhancer-binding factor family. The canonical Wnt pathway is crucial in cardiac development but has also been proposed as the key mechanism in certain cardiomyopathies (ie, activation induces cardiac hypertrophy). Therefore, N-cadherin has been thought to sequester  $\beta$ -catenin to prevent Wnt activation. Activation of the Wnt pathway increases expression of the GJ protein Cx43, and the C-terminus of Cx43 can interact with  $\beta$ -catenin. When Wnt is not present, cytoplasmic  $\beta$ -catenin is targeted for degradation by the proteasome.



**Figure 18** Disease mechanisms for arrhythmogenic cardiomyopathy. Cardiomyocyte showing the extracellular matrix, sarcolemma, sarcomere, nucleus, and key proteins that provide structure for ventricular function and cardiac rhythm. See the description of the functions of these proteins in Section 4.1 Desmosomal Defects.

Although AJs also transduce forces to the cytoskeleton, desmosomes are more robust, thanks to their connection to mechanically resilient IFs. The intercellular part of the cardiac desmosome is built up by the cadherins desmoglein-2 (DSG2) and desmocollin-2 (DSC2), which bind in a heterologous way. The armadillo proteins junction plakoglobin (JUP) and plakophilin-2 (PKP2), and desmoplakin (DSP) (a member of the plakin superfamily), connect desmin to the desmosome. When DSC2 and DSG2 are bound, the hyperadhesive state of the desmosome depends on the presence of calcium ions.

Considering the major desmosomal proteins, PKP2 is associated with GJs and is required for the organization of ID and desmosomal function. Together with JUP, PKP2 mediates attachment to IFs. PKP2 knockdown causes a decrease in conduction velocity and an increased propensity to develop re-entry arrhythmias, whereas PKP2 variants are most common in hereditary ACM. Plakoglobin is present in both desmosomes and AJs. Desmoplakin connects the desmosomes to the type III IF protein desmin, and its N-terminal and C-terminal domains and the  $\alpha$ -helical domain in between are each almost 1000 amino acids long and interaction with

PKP2 occurs at their N-terminal domains. DSG2 pathogenic gene variants are, like all other cardiac desmosomal proteins, associated with ACM.

The most prominent ACM desmosomal gene mutations include PKP2 and DSP, with desmosomal cadherins DSG2 and DSC2, and JUP being less common.<sup>14,25,169,265</sup> The majority of these genes primarily cause ARVC, although pathogenic variants in DSP cause a substantial amount of ALVC. Other “nondesmosomal” genes, such as TGFβ3 and TMEM43, disrupt the function of desmosomes.<sup>132,266,267</sup> One of the more recently described causative genes is CDH2, encoding N-cadherin, another member of the cadherin superfamily of predominantly Ca<sup>2+</sup>-dependent cell surface adhesion proteins.<sup>118,119</sup> In the report by Mayosi et al, the affected family members all presented with ventricular arrhythmias and demonstrated imaging features of ARVC. The study by Turkowski et al, however, described a family with an arrhythmogenic presentation who all showed a cardiomyopathy in the imaging study.<sup>119</sup> In desmosomes, desmosomal cadherins (desmocollin and desmoglein) are mainly anchored to the IFs of the cytoskeleton through numerous intracellular

protein partners, whereas in fascia AJs, the classical cadherin N-cadherin is primarily anchored to the actin microfilaments of the cytoskeleton and promotes cell–cell adhesion through extracellular associations of its cadherin repeat domains.<sup>268–270</sup> Interestingly, the protein components of desmosomes and fascia AJs are not mutually exclusive.<sup>270,271</sup> In fact, the mechanical junctions of the ID are an admixture of desmosomal and fascia adherens proteins that form a hybrid functional zone, the area composita.<sup>269,272,273</sup> Therefore, even if ARVC has been traditionally considered as a desmosomal disease, it is now reasonable to consider that the mechanistic basis of ARVC may extend beyond the strict functional zone of the desmosome, to that of the area composita. Supporting this concept, pathologic variants in *CTNNA3* (another gene in the area composita), which encodes for  $\alpha$ T-catenin, has also been identified in patients with ARVC who were negative for pathologic variants in the main desmosomal genes.<sup>115</sup>  $\alpha$ -catenins are natural partners of the cytoplasmic domain of classical cadherins, that is, N- and E-cadherins, and, in the case of N-cadherin, act as its go-between for anchoring to the actin cytoskeleton.

The fact that cadherin-2, like its desmosomal cadherin counterparts, is a major player in the ID is also supported by the *Cdh2* cardiac-specific mouse model with deletion of N-cadherin in the adult mouse heart causing dissolution of the ID structure, including loss of both desmosomes and AJs, demonstrating that desmosome integrity is also cadherin-2 dependent.<sup>274</sup> These mice also exhibited modest, albeit atypical, DCM and spontaneous ventricular arrhythmias that resulted in SCD.<sup>274</sup> This increased arrhythmic propensity (all mice experienced SCD approximately 2 months after deleting N-cadherin from the heart) was probably due to a reduced and heterogeneously distributed connexin-43, causing loss of functional GJs and partial cardiomyocyte uncoupling and highlighting the prominent role of cadherin-2 in all types of functional junctions in the ID.<sup>275</sup> GJ decreases in number and size, with concomitantly increased arrhythmia susceptibility, have also been demonstrated in the context of N-cadherin heterozygous null mice, with 30%–60% of these mice developing VT, suggesting that cadherin-2 haploinsufficiency might create an important arrhythmogenic substrate.<sup>276</sup> ID remodeling with concomitant reduction of localization of desmosomal proteins, connexin-43, and cadherin-2 has also been demonstrated in ventricular tissues of transplanted hearts of patients with ARVC, further supporting the involvement of cadherin-2 in ARVC pathogenesis.<sup>277</sup>

## 4.2. Ion channel defects

Cardiac cells are excitable cells that can generate and propagate an AP, the electrical signal that induces cardiomyocyte contraction. The cardiac AP is generated by ions moving across the cell membrane that, by depolarization, takes the cell from the resting state to an activated state and then, by repolarization, back to the resting membrane potential.<sup>278</sup>

All phases of the cardiac AP occur via the synergistic activation and inactivation of several voltage-dependent ion channels. In contractile cardiomyocytes, APs are triggered by the acute entrance of sodium ions ( $\text{Na}^+$ ) inside the cell, resulting in an inward current ( $I_{\text{Na}}$ ) (*SCN5A*) that shifts the membrane potential from its resting state ( $-90$  mV) to a depolarization state ( $+20$  mV). This phase is followed by the efflux of potassium ( $\text{K}^+$ ) ions through an outward current named  $I_{\text{to}}$ , which initiates cell repolarization. This in turn is followed by the plateau phase, a short period of constant membrane potential due to the balance between inward calcium ( $\text{Ca}^{2+}$ ) currents ( $I_{\text{CaL}}$ ) through the voltage-dependent L-type calcium channels (LTCCs) and time-dependent delayed-rectifier outward  $\text{K}^+$  currents (mainly slow delayed-rectifier  $I_{\text{Ks}}$  [*KCNQ1*] and rapid delayed-rectifier  $I_{\text{Kr}}$  [*KCNH2*]). At this point, the  $\text{Ca}^{2+}$  entry through the LTCC triggers a much larger release of  $\text{Ca}^{2+}$  from sarcoplasmic reticulum (SR) stores through the ryanodine receptor channel type 2, producing a systolic increase in the intracellular  $\text{Ca}^{2+}$  needed for cell contraction. Upon LTCC inactivation, the net outward  $\text{K}^+$  currents repolarize the cell and bring the membrane potential to its resting state. The balance between  $\text{Ca}^{2+}$  and  $\text{K}^+$  currents therefore determines the AP duration. The basal and acetylcholine-dependent inwardly rectifying  $\text{K}^+$  currents ( $I_{\text{K1}}$  and  $I_{\text{KACH}}$ ) control the final repolarization and determine the resting membrane potential.  $\text{Ca}^{2+}$  is then extruded from the cell through the  $\text{Na}^+/\text{Ca}^{2+}$  exchanger (NCX) type 1 and taken back into the SR through the SR  $\text{Ca}^{2+}$ -ATPase type 2a, thereby restoring low intracellular  $\text{Ca}^{2+}$  levels, allowing cell relaxation during diastole.

Pacemaker cells are distinct from other cell types in showing automaticity, a property resulting from both voltage-dependent and calcium-dependent mechanisms.<sup>279</sup> The former involves the funny current ( $I_{\text{f}}$ ) carried by hyperpolarization-activated cyclic nucleotide-gated channels,<sup>280</sup> which have several unusual characteristics, such as activation on hyperpolarization, permeability to sodium and potassium ions, modulation by intracellular cyclic adenosine monophosphate, and a small single-channel conductance. The latter involves spontaneous calcium release from the SR,<sup>281</sup> which activates  $I_{\text{NCX}}$ . The crucial role of calcium-dependent mechanisms has been demonstrated in mice with complete atrial-specific knockout of NCX, which has shown no pacemaker activity.<sup>282</sup> Both mechanisms result in spontaneous depolarization responsible for the rising slope of the membrane potential. When the proper ion current flows are disturbed, electrical abnormalities in the form of arrhythmias occur.

### 4.2.1. *SCN5A*

The *SCN5A* gene, which encodes the alpha subunit of the voltage-gated sodium channel  $\text{Na}_v1.5$ , is responsible for the inward sodium current ( $I_{\text{Na}}$ ).<sup>283</sup> This current is the main component of rapid depolarization in cardiomyocytes and is responsible for the AP upstroke, which subsequently initiates the multistep excitation–contraction coupling cascade.<sup>284</sup>

This periodic depolarization underlies the synchronous and rhythmic contraction of the heart chambers.<sup>284</sup>

Pathologic variants in genes encoding for ion channel proteins are well-known causes of inherited arrhythmia disorders, such as LQTS, short QT syndrome (SQTS), BrS, CPVT, and AV block, to name a few. The involved genes include those encoding for the cardiac sodium channel, potassium channels, and calcium channels. In these disorders, pathologic variants in the affected gene result in disturbance of the function of the encoded ion channel protein, leading to abnormalities in the function of the AP. In several of these genes, pathologic variants can cause a heterogeneous array of clinical features, at times differing even within the same family. For instance, pathologic variants in the cardiac sodium channel gene *SCN5A* are responsible for LQTS type 3 (LQT3), which develops due to a gain in channel function. On the other hand, pathologic *SCN5A* variants also cause BrS, an electrocardiographically distinguishable disorder compared with LQT3, which occurs due to a loss of sodium channel function.<sup>285</sup> In addition to causing ventricular tachyarrhythmias, atrial fibrillation, atrial standstill, and AV block,<sup>286</sup> *SCN5A* is known to cause an arrhythmogenic form of DCM and an arrhythmogenic form of LVNC.<sup>287</sup>

The 2006 Scientific Statement on “Contemporary definitions and classification of the cardiomyopathies,” endorsed by the AHA, placed “ion channel disorders” under the classification of primary genetic cardiomyopathies.<sup>288</sup> This decision was largely based on data regarding the role of pathologic variants in genes encoding defective ion channel proteins, governing cell membrane transit of sodium, potassium, and calcium ions leading to ion channel-related arrhythmia disorders, including LQTS, SQTS, BrS, and CPVT and the role of these disorders in the development of cardiomyopathies.<sup>288</sup> This classification scheme has continued to be evaluated, and the list of overlapping cardiomyopathy–arrhythmia phenotypes has grown over time, with primary and secondary causes of ion channel dysfunction seen in many cardiomyopathies. Pathogenic variations in the *SCN5A* gene, resulting in electrical and structural cardiac remodeling, (ie, arrhythmogenic DCM), was first described in 2003 by Groenewegen et al in a large family with atrial standstill, a rare form of atrial cardiomyopathy.<sup>289</sup> At the same time, it was shown that the clinical spectrum of rare *SCN5A* pathologic genetic variants could be expanded to ARVC and DCM, accompanied by arrhythmias and conduction disorders.<sup>131,290</sup> In 2008, new evidence showed that pathologic variants in the *SCN5A* gene might represent a risk factor for rhythm disturbances in LVNC.<sup>291</sup> These disorders are inherited as autosomal dominant traits. The frequency of *SCN5A*-mediated cases in patients with ACMs is approximately 2%;<sup>292</sup> however, when pathologic variants in the *SCN5A* and *LMNA* genes are taken together, they account for up to 5%–10% when considering only patients with DCM with progressive cardiac conduction defects and supraventricular and/or ventricular arrhythmias. Both RV and LV dilation and dysfunction can occur, as can broad

and heterogeneous electrical abnormalities, including atrial standstill, progressive AV block, atrial fibrillation, sick sinus syndrome, VT, torsades de pointes, and VF, resulting in arrhythmic sudden death in some cases.

*SCN5A* may also play a role in ACM without having pathogenic gene variants. In ARVC, it is clear that when pathologic variants in genes encoding the cardiac desmosome are identified,  $Na_v1.5$ , which has been shown to coprecipitate with the desmosomal protein *PKP2*, can be disrupted and dysfunctional. The loss of *PKP2* expression has been shown to alter the amplitude and kinetics of the sodium current ( $I_{Na}$ ).<sup>293</sup> In addition, pathologic variants in *PKP2* have been associated with a sodium channelopathy phenotype, whereas decreased immunoreactive  $Na_v1.5$  protein has been detected in the majority of human ARVC heart samples.<sup>294</sup> These observations indicate a close functional association between  $Na_v1.5$  and mechanical junction proteins, which is further supported by the finding that  $Na_v1.5$  coprecipitates with the AJ protein N-cadherin<sup>295</sup> and demonstrating the presence of “adhesion/excitability” nodes formed by aggregates of  $Na_v1.5$  and N-cadherin.<sup>296</sup> Le-Macias et al described the presence of these adhesion/excitability nodes in cardiac myocytes and demonstrated that (1) the AJ protein N-cadherin serves as an attractor for  $Na_v1.5$  clusters, (2) the  $Na_v1.5$  in these clusters are major determinants of the cardiac sodium current, and (3) clustering of  $Na_v1.5$  facilitates its regulation by molecular partners.<sup>296</sup> Te Riele et al further demonstrated that  $Na_v1.5$  is in a functional complex with cell adhesion molecules and that a primary  $Na_v1.5$  defect can affect N-cadherin biology, resulting in reduced size and density of N-cadherin clusters at the ID.<sup>295</sup>

The finding that  $Na_v1.5$  coprecipitates with the AJ protein N-cadherin demonstrates the link to the junction/ID/desmosome and supports the hypothesis that sodium channel dysfunction can occur via disruption of binding partners being mutated (ie, supporting the *PKP2* and arrhythmia scenario). Therapy for this disorder has not been well studied and is not standardized. Pacemakers and ICDs have been used for some individuals with varying outcomes. Pharmacological therapies have been disappointing, and no specific pharmacotherapy has thus far been recommended for these patients.

### 4.3. Cytoskeletal defects

The cytoskeleton is the cell’s basic scaffold in which other subcellular components are spatially arranged so as to communicate efficiently between the cell’s internal and external environments. In striated muscle cells, the cytoskeleton consists of myofibrillar and extramyofibrillar portions. The myofibrillar cytoskeleton is composed of thin and thick myofilaments and titin filaments, providing the foundation for myocyte contraction and relaxation. The extramyofibrillar cytoskeleton consists of microfilaments, microtubules, and IFs.

IFs serve as a scaffold connecting the sarcomere to other organelles (such as mitochondria or the nucleus) to maintain

cellular integrity and contribute to mechanotransduction. The sarcomere is tethered to the sarcolemma (the membrane surrounding the myofibril) by another cytoskeletal assembly—the costamere. Costameres link the sarcomere to the sarcolemma via the Z-disc and M-band. Individual heart cells are connected by IDs, which synchronize muscle contraction. The myofibrils are linked to the plasma membrane at the Z-discs via the costameres. There are specific membrane invaginations (T-tubules) at the Z-disc, which associate with flanking SR to the dyad. At the ID, desmosomes and AJs link neighboring cardiomyocytes mechanically, and GJs provide ion channels for intercellular communication. Desmosomes link to the IF cytoskeleton (composed of desmin), whereas AJs anchor actin filaments (the myofibrils). The border of the last sarcomere before the plasma membrane is defined as the transitional junction.

The cytoskeletal structure is continually remodeled to accommodate normal cell growth and respond to pathophysiological cues. The cytoskeleton maintains the structural integrity and morphology of cardiomyocytes. Cytoskeleton components are also involved in a variety of cellular processes, such as cell growth and division, cell movement, vesicle transport, cellular organelle location and function, localization and distribution of membrane receptors, and cell–cell communications. The cytoskeleton in cardiac myocytes is also believed to play an important role in the transduction of mechanical signals, based upon the unique distribution of the extensive cytoskeletal network as well as the juxtaposition of ion channels, signaling transducers, and network messengers. Cytoskeletal modifications and cardiac myocyte remodeling are causally linked to cardiac hypertrophy and failure. Abnormalities in cytoskeletal components not only cause structural defects but also impair mechanotransduction. The cytoskeleton not only interacts with the extracellular matrix via transmembrane proteins such as integrins but also registers adjacent Z-discs to one another, to the cell membrane, and to the nuclear envelope through a delicate network. A number of signaling partners bind to the network either directly or via linker proteins. For example, the muscle LIM protein (MLP) gene encodes a muscle-specific cytoskeletal protein interacting with titin and telethonin (T-cap). Studies in genetically engineered mice with targeted ablation of MLP suggest that the titin–telethonin–MLP complex may serve as a stretch sensor in cardiac muscle cells. There is growing interest in examining the role of cytoskeletal components in ion channel regulation under physiological and pathological conditions.

DCM characterized by ventricular dilatation and diminished contractile function accounts for more than 80% of non-HCMs. DCM has a population prevalence of approximately 1 in 500 and is associated with prognostically adverse arrhythmias at initial disease presentation in up to one-third of patients.<sup>297</sup> While increased age, male sex, and impaired ventricular function are established arrhythmic risk factors, arrhythmias also occur in patients with no known risk factors. Approximately 20%–35% of DCM cases are familial. Although impaired force generation, energy shortage, and

compromised calcium homeostasis could cause DCM, impaired force transmission and/or defective mechanotransduction caused by defects in cytoskeletal proteins such as desmin, lamin A/C,  $\alpha$ -actin,  $\delta$ -sarcoglycan, dystrophin, plakoglobin, desmoplakin, MLP, and telethonin appear to be a prevalent mechanism underlying DCM.

#### 4.3.1. Myofibrillar cytoskeleton

The myofibrillar cytoskeleton is composed of thin and thick myofilaments of the sarcomere as well as titin filaments, providing the foundation for myocyte contraction and relaxation. The basic unit of a myofibril is called the sarcomere and is defined as the region between two Z-discs. The actin cross-linker protein  $\alpha$ -actinin is a classical marker for Z-discs; however, Z-discs house a large number of other cytoskeletal and signaling proteins. The sarcomere, which is the smallest contractile unit of striated muscle, has its lateral boundaries defined by the protein-dense Z-discs that cross-link the barbed ends of actin-based thin filaments from adjacent sarcomeres via  $\alpha$ -actinin and are bordered by the I-band, the region on either side of a Z-disc that is devoid of myosin-containing thick filaments. The A-band comprises the region extending the entire length of the thick filaments, and the M-band resides at the center of the A-band. The force of muscle contraction occurs when the myosin motor protein attaches to the actin filament and pulls the Z-discs toward the M-band. The sarcomere is not a static structure and responds to alterations in muscle load and injury. Z-discs also serve as an anchor site for the N-terminus of titin and nebulin and nebulin filament systems, making it indispensable for transmitting contractile force.

Z-discs anchor the thin filaments, which are composed of actin, tropomyosin, and the troponin complex. Tropomyosin and the troponin complex are crucial for contraction regulation at the thin filament level, which is triggered by calcium. The thick filaments are composed of myosin dimers (a myosin consists of a myosin heavy chain and two myosin light chains), which are arranged in bipolar filaments, with the myosin tails making up the central region of the sarcomere and the head interdigitating with the thin filaments. Myosin-binding protein C is associated with a subset of the myosin heads and contributes to controlling contraction at the thick filament level. The third filament system is called the elastic filaments and consists of titin.

Variants in Z-disc-associated proteins are linked to numerous cardiomyopathies and skeletal myopathies.<sup>298–301</sup>  $\alpha$ -actinin is the predominant Z-disc protein. There are four vertebrate  $\alpha$ -actinin genes with overlapping functions; however, only *ACTN2* is found in cardiac muscle.<sup>302</sup> The N-terminal actin-binding domain is linked to an  $\alpha$ -actinin-2 homodimer cross-linking two antiparallel actin filaments of adjacent sarcomeres, forming a flexible tetragonal lattice.<sup>303</sup> This lattice is essential for the rigidity that the Z-disc requires to serve as a structural anchor site, while still allowing for the flexibility needed to conform to contractile forces.

$\alpha$ -actinin has a myriad of binding partners, with each interaction serving a distinct role in the production of concerted

contractile action. The major Z-disc proteins that interact with ACTN2 include actinin-associated LIM protein, muscle LIM protein, the N-terminus of titin, myotilin, CapZ, Z-band alternatively spliced PDZ-motif protein (ZASP), filamin,  $\alpha$ -actinin, and telethonin-binding protein at the Z-disc, myopalladin, and myopodin.<sup>304–306</sup> Independent studies have reported that human variants in the *ACTN2* gene are associated with DCM, HCM, idiopathic VF, LVNC, and atrial arrhythmias.<sup>307</sup>

Filamin protein family members also bind and cross-link actin. There are three filamin proteins: filamin-A ( $\alpha$  isoform), filamin-B ( $\beta$  isoform), and striated muscle-specific filamin-C ( $\gamma$  isoform). Filamin-C ( $\gamma$ -filamin) is one of the major proteins that serves as a link between the costamere and Z-disc and is involved in signal transduction with integrins. Filamin-C functions through interactions with sarcolemmal muscle cell membrane proteins such as  $\gamma$ - and  $\delta$ -sarcoglycans of the dystrophin glycoprotein complex,<sup>308</sup> the  $\beta$ 1A-subunit of the integrin receptor complex,<sup>309</sup> and Z-disc proteins (such as myotilin<sup>310</sup> and FATZ<sup>309,311,312</sup>). An autosomal dominant nonsense variant, p.Trp2710\*, in the last exon of the human filamin-C gene interferes with its dimerization process and causes filamin-C to aggregate within skeletal muscle fibers, a phenomenon that eventually leads to myofibrillar myopathy.<sup>313,314</sup>

Many of the proteins within the myofibrillar cytoskeleton have been shown to cause cardiac and/or skeletal myopathy. Review of the details on the patients with pathologic variants in the genes encoding these proteins with disturbance of protein function has demonstrated a significant association with early-onset arrhythmias, conduction system disease, and sudden cardiac arrest or death, consistent with an arrhythmogenic form of cardiomyopathy.

#### 4.3.2. *ZASP/LDB3*

ZASP/LIM domain binding 3 (LDB3) is one of the major components of the Z-disc proteins in cardiac muscle<sup>315</sup> and plays an important role in stabilizing the Z-disc structure through its PDZ-mediated interaction with  $\alpha$ -actinin-2, the main component of the Z-disc actin cross-linker, and F-actin, the main cytoarchitectural protein of cardiomyocytes.<sup>316</sup> Global ablation of the murine ZASP homolog cypher can disorganize the sarcomere and cytoskeleton, leading to severe cardiomyopathy and skeletal myopathy in mice and humans,<sup>317</sup> whereas cardiac-specific ablation of cypher can cause DCM and SCD.<sup>318</sup> The product of *SCN5A*, the  $\text{Na}_v1.5$  current, localizes at the cardiomyocyte membrane along the sarcomeric Z-lines via  $\alpha$ -actinin-2, thus connecting  $\text{Na}_v1.5$  to actin filaments.<sup>319</sup> ZASP/telethonin contributes to localizing  $\text{Na}_v1.5$  to the T-tubule membrane at the Z-line, creating a multiprotein complex associated with  $\alpha$ -actinin-2. Variants in the *ZASP/LDB3* gene have been shown to cause abnormalities in sodium channel function.

Vatta et al were the first to describe pathologic variants in *ZASP/LDB3* in patients with DCM and LVNC, identifying 6 (6%) of 100 probands screened.<sup>126</sup> Pathologic variants in

*ZASP/LDB3* were identified in 2 families and 4 sporadic cases. Of the 9 familial and sporadic patients affected, 3 had early-onset conduction system abnormalities and ventricular arrhythmias, including sinus bradycardia, second-degree AV block, PVCs, VT, intraventricular conduction delay, ventricular bigeminy, and LBBB. Subsequent reports on patients with arrhythmias and conduction disease associated with DCM and LVNC have supported the causative connection with variants in *ZASP/LDB3*. Arimura et al<sup>320</sup> reported on a family with 6 affected members who developed DCM between 50 and 69 years of age, consistent with late-onset DCM, 3 of whom died suddenly. Xi et al<sup>321</sup> studied one of the original *ZASP/LDB3* pathologic variants reported by Vatta et al<sup>126</sup> and demonstrated several underlying mechanisms by which the *ZASP-D117N* variant (a *ZASP/LDB3* variant identified in patients with DCM/LVNC associated with intraventricular conduction delay, ventricular bigeminy, and LBBB) can cause intraventricular conduction delay: (1) ZASP1-D117N can cause loss of function of  $\text{Na}_v1.5$  in human cell lines, and in neonatal cardiomyocytes; (2) in silico simulation using the Luo-Rudy model showed that the extent of functional disturbances of  $\text{Na}_v1.5$  caused by *ZASP-D117N* is sufficient to delay cardiac conduction in human hearts; (3) the interaction between ZASP and  $\text{Na}_v1.5$  requires preservation of the Z-disc protein complex; and (4) the modification of  $\text{Na}_v1.5$  by ZASP-D117N occurs without significant disruption of Z-line structures in cardiomyocytes.<sup>321</sup>

Although  $\text{Na}_v1.5$  preferentially localizes at the ID via SAP97 and LMs via the dystrophin-associated protein complex (2 pools), localization at the T-tubular system also occurs.<sup>322,323</sup> Upon posttranslational modification,  $\text{Na}_v1.5$  remains attached to the cytoskeleton linked to multiprotein complexes and stored in subcellular compartments.  $\text{Na}_v1.5$  is also known to localize at the cardiomyocyte membrane along the sarcomeric Z-lines via  $\alpha$ -actinin-2, thus connecting  $\text{Na}_v1.5$  to actin filaments.<sup>319</sup> The study by Xi et al therefore suggests that electrical remodeling may precede anatomical remodeling in DCM/LVNC associated with ZASP with the loss of function of  $\text{Na}_v1.5$  by the mutated ZASP, occurring without significant disruption of cytoarchitectural networks.<sup>321</sup> This is particularly important in a clinical situation, since patients who carry *ZASP-D117N* may develop arrhythmias even before manifesting HF symptoms. The loss of function of  $\text{Na}_v1.5$  by ZASP-D117N appeared to be largely responsible for the conduction delay.

More recently, Lopez-Ayala et al reported on a family in which a pathologic variant in *ZASP/LDB3* was associated with ARVC.<sup>158</sup> The index patient and her first-degree and second-degree relatives underwent a complete clinical evaluation. After ruling out pathologic variants in the 5 desmosomal genes, genetic testing using NGS was performed on the proband, who had a long-standing history of presyncope. The proband experienced syncope associated with sustained VT that required electrical cardioversion to restore sinus rhythm. Her ECG showed complete right bundle branch block (RBBB), with inverted and flat T waves in the

precordial leads. Echocardiogram and CMR showed biventricular dilation and severe biventricular systolic dysfunction; midwall LGE affecting the LV was also identified. An ICD was recommended. However, the patient died in the operating room during the surgical procedure as a result of an anesthetic complication. The postmortem examination demonstrated extensive fibro-fatty replacement in the RV, extensive fibrosis in the LV, and limited inflammatory patches, consistent with a diagnosis of ARVC. A heterozygous pathogenic missense variant in *ZASP/LDB3* (c.1051A>G) was identified, and another 6 carriers were identified in her family via cascade screening. Three of these relatives fulfilled the criteria for a definitive diagnosis of ARVC, and another reached a borderline diagnosis. These relatives had symptoms including frequent palpitations, abnormal ECGs that showed inverted T waves in right precordial and inferior leads, signal-averaged ECGs that showed late potentials, 24-hour Holter monitoring studies that showed runs of idioventricular rhythm and ventricular ectopic beats, CMR that showed a dilated RV with severe systolic dysfunction, and normal LV with no LGE. A number of the relatives were started on beta-blockers. On the basis of this family, the authors suggested a direct link between ACM with biventricular involvement and pathogenic variants in *ZASP/LDB3*.

#### 4.3.3. $\alpha$ -actinin-2

$\alpha$ -actinin-2 (ACTN2) is a prominent member of the Z-disc found in cardiac muscle, has an N-terminal actin-binding domain, and creates a lattice-like structure that is essential for the rigidity that the Z-disc needs to serve as a structural anchor site, while still allowing for the flexibility needed to be responsive to contractile forces.<sup>303,324,325</sup> The protein's primary function is to anchor and crosslink actin filaments in the cardiac Z-disc at the lateral boundaries of the sarcomere.<sup>306</sup> The Z-disc provides structural support by tethering the sarcomere to the sarcolemma via the costameres and by anchoring filamentous F-actin, titin, and nebulin.<sup>305</sup>

As one of the integral Z-disc proteins,  $\alpha$ -actinin has a myriad of binding partners, with each interaction serving a distinct role in the production of concerted contractile action.<sup>306</sup> The major Z-disc proteins that interact with  $\alpha$ -actinin-2 and  $\alpha$ -smooth muscle actin (ACTA2) are actinin-associated LIM protein, muscle LIM protein, the N-terminus of titin, myotilin, CapZ, ZASP, filamin, and telethonin-binding protein at the Z-disc, myopalladin, and myopodin. ACTA2 has also been demonstrated to bind phosphorylase-b, an important metabolic enzyme in the Z-disc. Furthermore, there is evidence that ACTN2 directly interacts with cardiac ion channels (such as the potassium ion channels KCNA4 and KCNA5<sup>326,327</sup> and the sodium ion channel SCN5A<sup>319</sup>) and forms a bridge between the calcium ion channels CACNA1C and CACNA1D.<sup>328</sup> Thus, disruption of ACTN2 may affect the localization and function of cardiac ion channels. The authors speculated that the

various clinical presentations of Ala119Thr result from a stochastic disruption of one of the many functional roles of ACTN2.

One presentation of ACM was reported by Bagnall et al, who performed exome sequencing on a four-generation family with idiopathic VF, LVNC, and sudden death and identified a pathologic variant in the ACTN2 gene.<sup>329</sup> Clinical evaluation of the family identified marked cardiac phenotype heterogeneity, with some individuals being asymptomatic and others having LVNC, resuscitated cardiac arrest due to idiopathic VF, DCM, or sudden unexplained death. WES identified an Ala119Thr pathologic variant in ACTN2 that segregated with disease. The 22-year-old female proband presented with syncope and a family history of premature sudden unexplained death (her 25-year-old sister died in her sleep). The proband's ECG showed sinus rhythm with nonspecific ST-T wave changes, and her echocardiogram and CMR showed prominent LV apical trabeculations with preserved LV systolic function, consistent with LVNC. There were no inducible arrhythmias in the EPS, and her QTc measured 440 ms. The proband was implanted with an ICD. Her father had a history of dyspnea, LBBB, and LV dilation with reduced LVEF of 27%. One of the proband's female cousins experienced a resuscitated cardiac arrest and her CMR revealed normal LV and RV indexed dimensions and function, with no evidence of myocardial fibrosis. The cousin was found to have idiopathic VF and was implanted with an ICD, which subsequently delivered two appropriate shocks. She responded successfully to quinidine therapy.

In another report, Girolami et al assessed a large 4-generation Italian family, 18 members of which underwent direct clinical assessment and genetic testing, including the proband.<sup>330</sup> Eleven individuals had evidence of autosomal-dominant cardiomyopathy and had variable combinations of 3 distinctive features: regional LV noncompaction with LV hypertrophy, atrial septal defect, and early-onset supraventricular arrhythmias and AV block. In most of these patients, frequent premature atrial contractions that developed into atrial fibrillation or flutter represented the initial clinical manifestation. These arrhythmic manifestations were an essential part of the phenotypic spectrum. The onset of supraventricular arrhythmias followed a common pattern, initially presenting with very frequent premature atrial contractions, proceeding to paroxysmal atrial fibrillation (between 30–50 years of age) and then to permanent atrial fibrillation, requiring a pacemaker due to slow ventricular conduction. Many of the family members were treated with ICDs. The authors suggested that the ACTN2 pathologic variants may directly participate in the genesis of familial supraventricular arrhythmias.

#### 4.3.4. Filamin-C

Filamin protein family members also bind and cross-link actin. There are 3 filamin proteins, with filamin-C ( $\gamma$  isoform) the only striated muscle-specific protein. In addition to the N-terminal actin-binding domain, there is a Z-disc



localization motif.<sup>310</sup> Filamin-C is one of the major proteins that serves as a link between the costamere and Z-disc and is involved in signal transduction with integrins. Filamin-C directly interacts with 2 protein complexes that link the subsarcolemmal actin cytoskeleton to the extracellular matrix: the dystrophin-associated glycoprotein complex and the integrin complex. At IDs, filamin-C is located in the fascia adherens where myofiber ends reach the sarcolemma, adjacent to the position of desmosomal junctions. Filamin-C functions through interactions with the sarcolemmal muscle cell membrane dystrophin-associated glycoproteins (such as  $\gamma$ - and  $\delta$ -sarcoglycans<sup>308</sup>), the  $\beta$ 1A-subunit of the integrin receptor complex, and Z-disc proteins (such as myotilin<sup>310</sup> and FATZ<sup>309,311,312</sup>). The participation of filamin-C in the attachment of the sarcomere's Z-disc to the sarcolemma (costameres) and to the IDs allows cell-to-cell mechanical force transduction. FLNC pathologic variants have been associated with myofibrillar myopathies, as well as cardiomyopathies.

Ortiz-Genga et al studied the *FLNC* gene using NGS in 2877 patients with inherited cardiovascular diseases,<sup>34</sup> with clinical and genetic evaluation of 28 affected families. The authors identified a characteristic phenotype in probands with truncating variants in *FLNC*, as well as 23 truncating pathologic *FLNC* variants in 28 probands previously diagnosed with DCM, ACM, or RCM. The authors also identified 54 pathologic variant carriers among 121 screened relatives. The phenotype consisted of LV dilation (68%), systolic dysfunction (46%), and myocardial fibrosis (67%) in the imaging test, as well as inferolateral negative T waves, low QRS voltages, and ventricular arrhythmias (82%) in the ECG (33%), with frequent SCD (40 cases in 21 of 28 families). The authors observed no clinical skeletal myopathy. Penetrance was >97% in carriers over 40 years of age, and there was an autosomal dominant inheritance pattern. Immunohistochemical staining of myocardial tissue showed no abnormal filamin-C aggregates in patients with truncating *FLNC* pathologic variants. Isolated or predominant RV involvement, common with desmosomal pathogenic variants, was not observed. Unlike patients with pathogenic lamin A/C, emerin, or desmin pathogenic variants, these patients had mild and infrequent cardiac conduction abnormalities. The authors suggested consideration of prompt implantation of a cardiac defibrillator for affected patients harboring truncating pathogenic variants in *FLNC*.

#### 4.3.5. Extramyofibrillar cytoskeleton

The extramyofibrillar cytoskeleton consists of microfilaments (actin), microtubules, and IFs (desmin). It connects the sarcomere with the sarcolemma and extracellular matrix through the Z-disc and submembrane cytoskeleton,<sup>331–334</sup> thereby ensuring power transmission produced by the sarcomeres. The extramyofibrillar cytoskeleton also provides support for subcellular structures, organizes the cytoplasm, regulates sarcolemma topography, and transmits intercellular and intracellular mechanical and chemical signals.

##### 4.3.5.1. Desmin filaments

Desmin is the main IF protein and is deemed necessary for cardiomyocyte structural integrity, the allocation and functionality of its mitochondria, the nucleus position, and sarcomere genesis.<sup>334,335</sup> The IFs create a 3-dimensional skeleton covering the entire cytoplasm, enveloping Z-discs, extending from one Z-disc to another. IFs are also involved with other cell organelles, including the SR and the T-tubular system. These desmin filaments extend from the Z-disc to the costameres, where they are bound through plectin and dysferlin, extend to the ID, and emerge from the Z-discs of the perinuclear myofibrils to the nuclear membrane.

Pathogenic variants in *DES*, encoding desmin, have been shown to cause severe skeletal and cardiac muscle diseases with heterogeneous phenotypes. *DES* variants have also been found in patients with DCM and ARVC. Brodehl et al<sup>336</sup> identified two novel variants in *DES* (p.Ala120Asp [c.359C>A] and p.His326Arg [c.977A>G]) in a family with a broad spectrum of cardiomyopathies, with a striking frequency of arrhythmias and SCDs. In vitro experiments with desmin-p.A120D identified a severe intrinsic filament formation defect causing cytoplasmic aggregates in cell lines and of the isolated recombinant protein. Model variants of codon 120 indicated that ionic interactions contributed to this filament formation defect. Ex vivo analysis of ventricular tissue slices revealed a loss of desmin staining within the ID and severe cytoplasmic aggregate formation, whereas Z-band localization was not affected. The authors proposed that the loss of desmin-p.A120D filament localization at the ID resulted in its clinical arrhythmogenic potential. Bermúdez-Jiménez et al more recently demonstrated impaired filament formation and disruption of cell membrane integrity in a severe form of arrhythmogenic LV cardiomyopathy due to a *DES* pathogenic variant, p.Glu401Asp, in a large family.<sup>337</sup>

Variants in the *DES* gene result in striated muscle disorders characterized by the formation of inclusion bodies, weakening of the desmin cytoskeleton, disruption of subcellular organelle organization, and eventually myofibril degradation. These muscle disorders are referred to as desmin-related myopathy or desminopathy and often present in young childhood, with patients experiencing increasing muscle weakness. These disorders are associated with a wide spectrum of clinical phenotypes, even within the same family, and range from scapuloperoneal, limb girdle, and distal myopathic phenotypes with variable cardiac or respiratory involvement to pure cardiomyopathies.<sup>338</sup>

To date, multiple reports of ACM caused by pathogenic *DES* variants have been published. *DES* variants have been previously reported in conduction disease and cardiomyopathies, in particular cases of DCM,<sup>339</sup> and, more recently, in ARVC.<sup>169</sup> The first of these, *DES* pathogenic variant p.N116S, was identified in a 17-year-old patient with ARVC and concomitant subclinical skeletal muscle alterations, and this variant led to an amino acid substitution that in turn led

to aggregates formation in cardiac and skeletal muscle.<sup>340,341</sup> All other reported ARVC-related *DES* variants underlie a clinically heterogeneous phenotype, frequently associated with muscle abnormalities, including a *DES*-p.S13F pathogenic variant identified in 39 family members from 8 Dutch families<sup>169,342</sup> with associated variable skeletal myopathy and a wide spectrum of cardiomyopathies, including 2 patients with ARVC. Another *DES* variant, p.N342D, was described in patients affected with desmin-related myopathies.<sup>343</sup> The association of this variant with RV cardiomyopathy was also noted in select patients.<sup>342,344</sup> A *DES*-p.P419S variant was identified by exome sequencing in a large Swedish family, showing myofibrillar myopathy and ARVC (ARVC7 locus).<sup>122</sup> Bermúdez-Jiménez et al described a multigenerational family in which approximately 30 family members affected with an ACM phenotype hosted a rare missense pathogenic variant of the *DES* gene (c.1203G>C; p.Glu401Asp).<sup>337</sup> These members showed that the *DES* Glu401Asp variant caused the disease in the family, with 100% penetrance and variable expressivity. The phenotype presented itself as an arrhythmogenic phenotype with a high risk of SCD and progressive HF. In 4 of the individuals studied, RV involvement was observed, and 2 had epsilon waves. Fibro-fatty infiltration was identified, predominantly in the LV, and the cardiomyocytes had reduced cellular adhesion, reminiscent of the defect found in ARVC, along with reduced expression of DES and cell–cell junction proteins.

#### 4.4. Sarcomeric defects

The cardiac sarcomere is the fundamental contractile unit of the cardiomyocyte. Genetic variants in sarcomere genes are a well-established cause of HCM and, in some cases, can cause familial DCM, LVNC, and RCM.<sup>345</sup> Variants in *MYBPC3* account for approximately 50% of all genotyped HCM cases, with most being loss-of-function variants, whereas missense variants in *MYH7* account for 30% of cases.<sup>346,347</sup> Other genes, such as *TNNT2*, *TNNI3*, *TPM1*, *ACTC1*, *MYL2* and *MYL3*, account for  $\leq 5\%$  of HCM cases each. A recent study investigating variant excess in cases compared with the Exome Aggregation Consortium control population<sup>348</sup> showed variants in *MYH7*, *TNNT2*, *TNNI3* and *TPM1* significantly enriched in patients with DCM.<sup>100</sup> Specifically, *MYH7* accounts for approximately 3%–4% of familial DCM cases.<sup>339</sup> Sarcomere gene variants contribute to cases of LVNC, although most often in phenotypes that include another cardiomyopathy, cardiac malformation and/or reduced ejection fraction, with *MYH7* variants contributing the most cases.<sup>349,350</sup> Other genes encoding sarcomeric and Z-disc proteins have also been identified in individuals with LVNC, including *ACTC1*, *MYBPC3*, *TNNT2*, *TPM1*, *TTN*, and *LDB3*. RCM in childhood can be caused by variants in thin filament genes, *TNNT2*, *TNNI3*, and *TPM1*.<sup>351</sup>

The presence of a sarcomere variant is associated with worse outcomes in HCM, with patients with sarcomere-positive HCM having poorer survival from major cardiovascular events compared with patients with gene-elusive HCM.<sup>347,352</sup>

Similarly, a recent study of LVNC cases showed a greater risk of major cardiovascular events in patients with a sarcomere variant compared with those without.<sup>353</sup> Using NGS, Wang et al targeted and sequenced 73 genes related to cardiomyopathy in 102 patients with LVNC, with 63% of pathogenic variants in sarcomere-encoding genes and 12% in ion channel-encoding genes.<sup>354</sup>

#### 4.5. Metabolic defects

The clinical manifestations of inherited disorders of fatty acid oxidation vary according to the enzymatic defect and can present as isolated cardiomyopathy (DCM, HCM), sudden death, progressive skeletal myopathy, and hepatic failure arrhythmias, which can be a presenting symptom of fatty acid oxidation deficiencies.<sup>355</sup> Over a 25-year period, Bonnet et al diagnosed 107 patients with an inherited fatty acid oxidation disorder; arrhythmia was the predominant presenting symptom in 24 (22%) of these patients.<sup>355</sup> These 24 cases included VT (n = 15), atrial tachycardia (n = 4), sinus node dysfunction with episodes of atrial tachycardia (n = 4), AV block (n = 6), and LBBB (n = 4) in newborn infants. The authors observed conduction disorders and atrial tachycardias in patients with defects of long-chain fatty acid transport across the inner mitochondrial membrane (carnitine palmitoyl transferase type II deficiency and carnitine acylcarnitine translocase deficiency) and in patients with trifunctional protein deficiency. Also, VTs were seen in patients with any type of fatty acid oxidation deficiency. The authors concluded that accumulation of the arrhythmogenic intermediary metabolites of fatty acids, such as long-chain acylcarnitines, could be responsible for the development of arrhythmias and that inborn fatty acid oxidation errors may cause unexplained sudden death or near-miss in apparently healthy infants and those with conduction defects or VT. Diagnosis is determined by a serum acylcarnitine profile.

Specifically, inborn fatty acid oxidation errors result in metabolite buildup proximal to the enzyme defect and in deficient formation of energy-yielding substrates after the block. In the defects downstream from carnitine palmitoyl transferase I, the acylcarnitine that accumulates has detergent properties, which may explain its toxicity. Indeed, amphiphilic lipid metabolite, long-chain acylcarnitine, and lysophosphatidylcholine accumulate during myocardial ischemia and play a pivotal role in the production of arrhythmias. Incorporation of long-chain acylcarnitine in the sarcolemma elicited electrophysiological anomalies analogous to those seen in acute myocardial ischemia.<sup>356</sup> The cellular electrophysiological bases of the proarrhythmic effects of long-chain acylcarnitine appear to be multifactorial. First, reduction of the single-channel conductance of the inwardly rectifying K current by amphiphilic lipid metabolites may account for automatic AP discharges from the resting and plateau potentials, leading to VT. Second, retardation of conduction velocities by the decrease in excitatory Na current could produce conduction anomalies and yield to reentry.<sup>357</sup> Third, nonesterified fatty acids directly activate voltage-dependent Na currents

in cardiac myocytes, inducing cytotoxic calcium overload.<sup>358</sup> Finally, amphipathic metabolites can interfere with the GJs and disturb the cell membrane's lipid-protein interface, thereby impairing GJ channels.<sup>359</sup> These toxic effects on ionic currents have not been observed with short- and medium-chain acylcarnitine.<sup>356</sup>

Systemic primary carnitine deficiency, a carnitine transporter deficiency, occurs when free carnitine cannot be freely filtered by renal glomeruli, in which 95% is supposed to be reabsorbed by the renal tubules by a high-affinity carnitine transporter in the cellular plasma membrane. Carnitine is not catabolized in humans, and its only metabolic conversion is through ester formation, with most esterified carnitine excreted in urine. Active carnitine transport from blood into cells is mediated by the same transporter that functions in the kidneys. The carnitine transporter OCTN2 is encoded by the *SLC22A5* gene and transports carnitine in a sodium-dependent manner.<sup>360,361</sup>

Carnitine transporter deficiency is inherited as an autosomal recessive trait. As a result of its deficiency, carnitine is not reabsorbed in the kidneys, leading to urinary loss and depletion of blood and tissue levels, resulting in severe impairment of long-chain fatty acid oxidation and hypoketotic hypoglycemia with fasting and stress. Age at presentation can range from infancy to adulthood, but neonatal hypoglycemia and sudden death can occur. Clinical manifestations in early-onset disease include chronic or acute skeletal myopathy and cardiomyopathy, typically exacerbated by metabolic decompensation. Untreated heart disease proceeds to DCM with reduced LVEF or mild interventricular septal hypertrophy. Electrocardiographic findings include abnormal T waves, ventricular hypertrophy, and atrial arrhythmias. Life-threatening arrhythmias can occur, including NSVT with periods of sinus rhythm and ventricular premature beats, even in the presence of only borderline LV hypertrophy. Carnitine supplementation is typically administered at a dose of 200 to 300 milligrams per kilogram body weight divided throughout the day.

#### 4.6. Mitochondrial forms

The presentation of mitochondrial cardiomyopathy includes HCM, DCM, and LVNC forms,<sup>362,363</sup> and the severity can range from asymptomatic to devastating multisystem disease.<sup>364</sup> Severe cardiac manifestations include SCD, HF, and ventricular tachyarrhythmia, which can worsen acutely during a metabolic crisis. Mitochondrial crises are often precipitated by physiological stressors such as febrile illness and surgery and can be accompanied by acute HF. Most patients with neuromuscular symptoms present with normal or slightly elevated creatine kinase levels, a normal electromyogram, and normal results of nerve-conduction studies.<sup>365–367</sup> Abnormal liver enzyme levels have been found in up to 10% of patients.<sup>365,368</sup> Sensorineural hearing loss occurs in 7%–26% of patients, and its prevalence increases with age.<sup>369,370</sup>

Patients with myoclonic epilepsy with ragged red fibers (MERRF) and mitochondrial encephalopathy, lactic acidosis,

and stroke (MELAS) should be monitored for the development of cardiac hypertrophy and DCM. Patients with MERRF can present with myoclonus, generalized convulsions, cerebellar ataxia, muscular atrophy, and elevated blood lactate and pyruvate levels, as well as ragged red fibers in muscle biopsy specimens. A case series of patients with MERRF and an m.8344A>G variant of mtDNA revealed that early age at onset was the only factor associated with the occurrence of myocardial disease.<sup>371</sup> The development of myocardial disease in this cohort was associated with a higher risk of SCD. Patients with MELAS can also present with ragged red fibers in the muscle biopsy; however, unlike patients with MERRF, patients with MELAS have normal early development and start to show symptoms only between 3 years of age and adulthood. Patients with MELAS tend to have short stature, seizures, hemiparesis, hemianopia, and blindness.<sup>372</sup>

Mitochondrial variants are common causes of myocardial LVNC in young children. LVNC is characterized by prominent ventricular trabeculations and deep recesses that extend from the LV cavity to the subendocardial surface of the ventricle, accompanied or not by LV dysfunction.<sup>373–375</sup> Studies have shown the importance of substrate flexibility in preserving normal cardiac function. In experimental models of pressure overload, failing human hearts have shifted from oxidizing fatty acids (the preferred substrate in the healthy heart) to oxidizing glucose for energy production. This metabolic switch is associated with the downregulation of genes involved in mitochondrial biogenesis and fatty-acid metabolism and is mediated by the deactivation of PPAR- $\alpha$  and its activator, PGC- $\alpha$ , which are members of a family of transcriptional coactivators involved in mitochondrial regulation and biogenesis. An increased reliance on glycolytic pathways could effectively reduce oxygen consumption in the short term; over time, however, reduced oxygen consumption might enable the progression of heart disease by creating an energy-deficient state.<sup>376</sup> Experimental evidence has shown that elevated fatty-acid flux and fatty-acid oxidation (FAO)-deficient states can be associated with cardiac dysfunction. Both chronic increases in FAO (as observed in diabetes) and decreases in FAO (as seen in pressure-overload models of HF) can lead to HF.<sup>377</sup> Accordingly, energy deficiency can be broadly conceived as both a cause and an effect of HF.

The management of mitochondrial disease and cardiomyopathy is largely supportive. Physicians should be aware that patients can make a remarkable recovery from a severe crisis state. Pharmacological strategies include the use of various dietary supplements. A typical “mitochondrial cocktail” would include coenzyme Q10, creatine, L-carnitine, thiamine, riboflavin, folate, and other antioxidants, such as vitamins C and E. Studies have suggested that the use of antioxidants partially improves clinical features.<sup>376,378</sup> In contrast, a systematic review by Chinnery et al found no clear evidence to support the use of any supplement in patients with mitochondrial disease.<sup>379</sup>

The mortality rate can be high for patients with mitochondrial disease that progresses to a crisis state, such as an acute or subacute multiorgan failure secondary to mitochondrial respiratory chain function that worsens due to fever, illness, stress, medications, or heat; urgent treatment is therefore necessary. Crises that can be associated with severe lactate elevations and cardiac complications during a crisis include cardiogenic shock, atrial and ventricular arrhythmias, DCM, and SCD. Patients often have baseline acidemia, and the correction of acidosis should be gradual. Oxygenation can worsen the crisis by increasing free-radical production; the partial pressure of oxygen therefore needs to be maintained between 50 and 60 mm Hg.<sup>380,381</sup> Patients with mitochondrial disease who present with fever or who are unable to eat or drink may be administered dextrose-containing intravenous fluids—preferably D10 with half-normal saline content—at a maintenance dose, regardless of blood glucose levels. Their metabolic and volume status should be evaluated periodically. The management of these patients' cardiac complications, including HF, bradyarrhythmias, and tachyarrhythmia, follows the same guidelines as those for the general population. If cardiac dysfunction is noted during a crisis, patients should be closely monitored using serial echocardiography. In selected patients who have advanced HF due to cardiomyopathy, cardiac transplantation may be needed. Three pediatric patients with mitochondrial cardiomyopathy who underwent cardiac transplantation reportedly had excellent early and late outcomes.<sup>382</sup>

#### 4.6.1. Kearns-Sayre syndrome

Kearns-Sayre syndrome (KSS) is a mitochondrial myopathy characterized by the clinical triad of ptosis, chronic progressive external ophthalmoplegia, and abnormal retinal pigmentation and is associated with cardiac conduction defects and DCM, sometimes requiring transplantation.<sup>383,384</sup> Approximately 50% of patients with KSS have cardiac involvement, including recurrent syncope, bundle branch block, fascicular block, and nonspecific intraventricular conduction disturbances; 20% of deaths in these patients have been attributed to cardiac causes. In a guidelines publication, the ACC/AHA/HRS assigned a class I recommendation (with a LOE B rating) to pacemaker implantation for third-degree and advanced second-degree AV block at any anatomic level when associated with neuromuscular diseases and AV block. Skeletal muscle histopathology commonly demonstrates ragged red fibers. The genetic abnormalities observed in KSS consist largely of single large-scale mitochondrial DNA deletions, although mitochondrial DNA point variants, such as m.3249G>A in the *tRNA (Leu)* gene, m.3255G>A in the *tRNA (Leu)* gene, and m.3243A>G in the *tRNA (Leu)* gene, have also been reported.<sup>384,385</sup>

#### 4.7. Histiocytoid (oncocytic) cardiomyopathy

Infantile histiocytoid cardiomyopathy is a rare but distinctive arrhythmogenic disorder characterized by incessant VT, cardiomegaly, and sudden death within the first 2 years of life if

left untreated. Approximately 100 histiocytoid cardiomyopathy cases have been reported in the literature;<sup>386–400</sup> however, the prevalence is likely to be higher, given that many cases of histiocytoid cardiomyopathy could have been misdiagnosed as sudden infant death syndrome.<sup>401</sup> Female preponderance is approximately 4:1, with most cases (90%) occurring in girls under 2 years of age, leading to intractable VF or cardiac arrest. The lesion resembles a hamartoma with histiocytoid or granular cell features.<sup>400</sup> The condition has clearly been defined as a mitochondrial disorder and affects the function of complexes I and III of the respiratory chain of the cardiac mitochondria.<sup>400</sup> The etiology favors either an autosomal recessive gene or an X-linked condition.

Histopathological findings in patients with histiocytoid cardiomyopathy include multiple flat-to-round, smooth, yellow nodules located beneath the endocardial surface of the LV, the atria, and the four cardiac valves. The nodules are composed of demarcated, large, foamy granular cells. Glycogen, lipids, and pigment may be observed in these cells, as well as a lymphocytic infiltrate. Immunostaining shows perimembranous immunoreactivity for muscle-specific actin, but not for the histiocytic markers, S-100 protein and CD69.<sup>387,391,398,402,403</sup> These cells may be abnormal Purkinje cells; however, a primitive myocardial precursor cannot be excluded. Radiofrequency ablation or pacemaker implantation may be required to treat arrhythmias.<sup>404</sup> Surgical intervention with prolonged survival has been reported.<sup>405</sup>

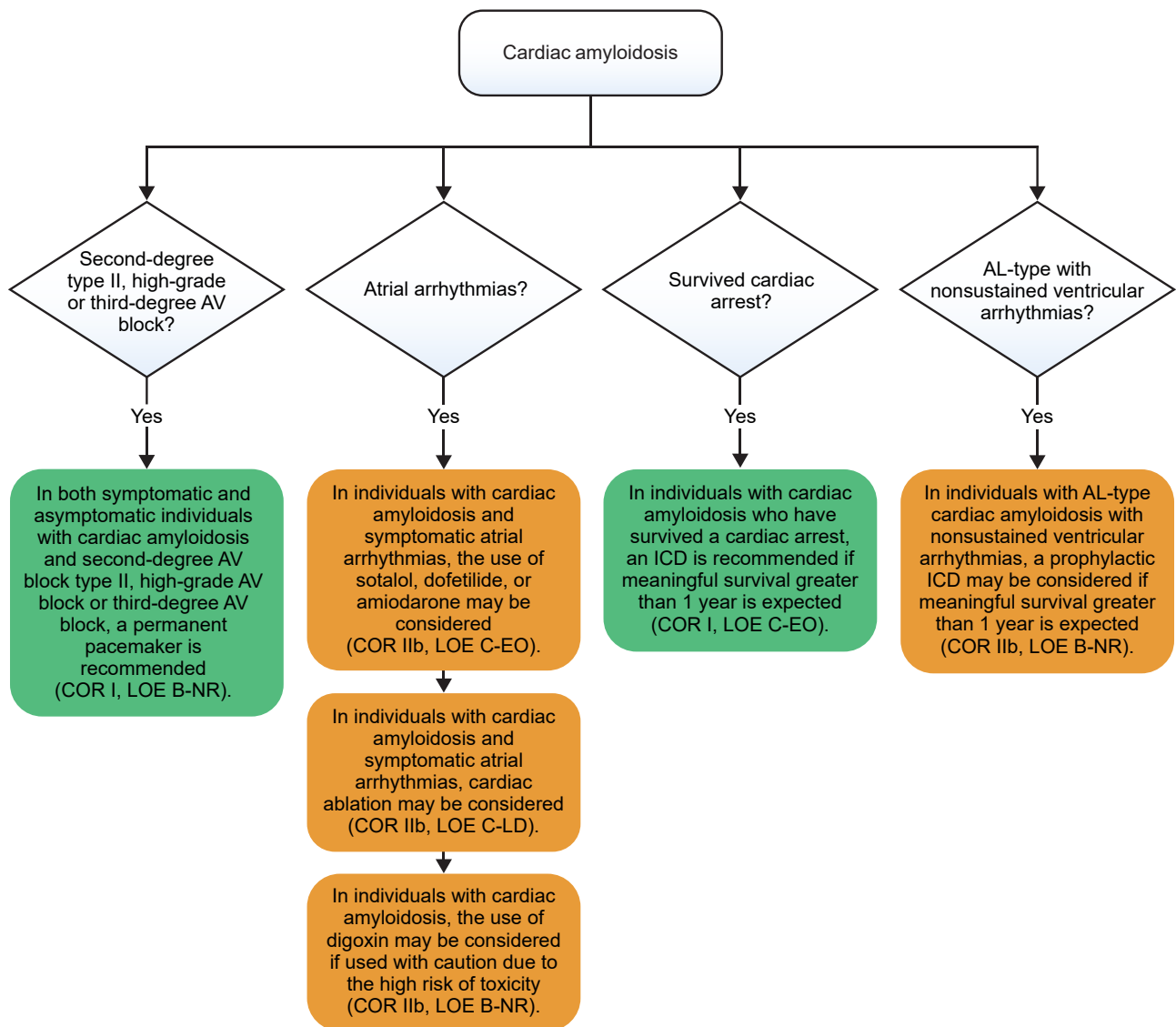
Shehata et al reported two probands with de novo nonsense variants in the X-linked nuclear gene *NDUFB11*, which had not previously been implicated in any disease, despite evidence that deficiency for other mitochondrial electron transport complex I members leads to cardiomyopathy.<sup>406</sup> A third proband was doubly heterozygous for inherited rare variants in additional components of complex I, *NDUFAF2*, and *NDUFB9*, confirming that histiocytoid cardiomyopathy is genetically heterogeneous. In a fourth case, the proband with histiocytoid cardiomyopathy inherited a mitochondrial variant from her heteroplasmic mother, as did her brother, who presented with cardiac arrhythmia. A causal role for *NDUFB11* truncation in the etiology of histiocytoid cardiomyopathy helps explain the disease's female bias. Whereas most complex I deficiencies are thought to be inherited in a Mendelian recessive manner, these two de novo variants establish a dominant haploinsufficient phenotype.

## Section 5 Other disorders

### 5.1. Infiltrative cardiomyopathies: amyloidosis

See Evidence Table: ACM Amyloidosis. A recommendation flow diagram is shown in [Figure 19](#).

Cardiac amyloidosis refers to the extracellular deposition of low molecular weight proteins within the myocardium, usually occurring in the context of more widespread organ involvement. The amyloid deposits are typically formed by one of two proteins: light chains or transthyretin.<sup>407,408</sup>



**Figure 19** Amyloidosis arrhythmia treatment recommendations. AL = amyloid light-chain; AV = atrioventricular; COR = Class of Recommendation; ICD = implantable cardioverter defibrillator; LOE = Level of Evidence. Colors correspond to COR in Figure 1.

Isolated atrial amyloidosis due to atrial natriuretic peptide deposition typically occurs in older age, and small studies have suggested its role in atrial fibrillation.<sup>409,410</sup> Light chain amyloidosis (AL amyloidosis) is secondary to a primary blood dyscrasia, which drives an abnormal proliferation of plasma cells and subsequently the monoclonal overproduction of light chains. Chemotherapy and stem cell transplantation have transformed care and vastly improved survival for AL amyloidosis.<sup>411</sup> Transthyretin amyloid is composed of a different protein, a misfolded prealbumin that will also produce amyloid fibrils and deposits in tissues.<sup>408</sup> Treatment includes liver transplantation, which can retard progression; the results are variable, however, and advanced multiorgan involvement often prevents curing. Newer therapies to stabilize transthyretin, diminish its production, or remove it from affected organs are currently under investigation.<sup>412–416</sup>

Cardiac involvement is in the form of an infiltrative cardiomyopathy in addition to HF via primarily diastolic limitation; small vessel disease,<sup>417</sup> conduction system disease,<sup>418–420</sup> and atrial and ventricular arrhythmias<sup>421</sup> are all well recognized. Histological evaluation of hearts with cardiac amyloidosis has provided insight into the potential underlying mechanisms of cardiac arrhythmia. Amyloid fibrils infiltrate the extracellular matrix, disrupting myocardial cellular arrangement and leading to myocardial fibrosis.<sup>422,423</sup> Perivascular amyloid infiltration and impairment of cardiomyocyte function are also well described,<sup>424,425</sup> and the subsequent impaired vasoreactivity can result in relative myocardial ischemia and abnormal electrical conduction. This cardiotoxic infiltrative milieu is hypothesized to be the fundamental driver of conduction abnormalities, atrial and ventricular arrhythmias. Although widespread involvement is not

uncommon, with sinus node dysfunction well-recognized,<sup>426–428</sup> infranodal conduction system disease appears to be the primary conduction abnormality, as evidenced by HV interval prolongation.<sup>418,429</sup> The disease is associated with the risk of sudden death in a number of cohorts.<sup>418</sup> Due to the progressive amyloid deposition throughout the heart, sinus node dysfunction and conduction disease often worsen, prompting the consideration for permanent pacemakers. For those patients for whom permanent pacing is necessary, lead placement should be carefully considered, given the potential for further LV depression related to RV pacing dyssynchrony. Currently, there are no studies that can provide definitive guidance on this issue.

Autonomic dysfunction with orthostatic presyncope or syncope is commonly observed in patients with systemic amyloid disease and cardiac involvement, and peripheral vasoconstrictors are frequently needed to manage symptoms.<sup>430–432</sup> A clear conduction abnormality needs to be considered as the etiology in these patients, recognizing that most cases of SCD are likely related to infranodal conduction disease. Furthermore, significant cardiac involvement with advanced infranodal conduction abnormalities can often be masked by a normal-appearing QRS complex.<sup>418,429</sup> By further blocking AV nodal conduction by preventing compensatory physiological heart rate recovery and directly preventing vasoconstriction, the actions of calcium blocking agents converge to create a malignant and potentially lethal combined effect. Evidence is limited, however, to small case series and 2 case reports.<sup>433–435</sup>

The most common tachyarrhythmia in this disorder is atrial arrhythmia. Rate control using AV nodal blocking agents can be especially challenging in the face of the relative hypotension and impairment in compensatory vaso-reactivity that is commonly seen with widespread systemic and autonomic impairment. AV nodal ablation has been evaluated and appears to be a reasonable consideration in more resistant and symptomatic cases.<sup>436</sup> Antiarrhythmic approaches are often necessary, given that maintenance of active atrial systole can be imperative for patients with restrictive LV filling; however, extensive amyloid infiltration, when present, could impair atrial systole. Extensive substrate abnormalities, presumably related to extensive atrial amyloid fibril infiltration, are common, and results from atrial fibrillation ablation are less than ideal.<sup>429,436</sup> Frequent ectopy with NSVT is the most common ventricular dysrhythmia, yet neither burden of ectopy nor NSVT appears to predict SCD.<sup>437</sup> Whether ICDs improve survival is not clear,<sup>438–442</sup> and progressive HF and terminal pulseless electrical activity remains a common theme associated with cardiac death in this group. This situation may be different for patients with cardiac amyloidosis who have been successfully managed for AL-type disease<sup>421</sup> and for patients awaiting cardiac transplantation; individualized approaches are therefore necessary.

Patients with cardiac amyloidosis remain at high risk for developing intracardiac thrombus and thromboembolic stroke;<sup>443,444</sup> anticoagulation needs to be carefully considered even in the absence of atrial arrhythmias.

COR	LOE	Recommendations	References
<b>I</b>	<b>B-NR</b>	<b>In both symptomatic and asymptomatic individuals with cardiac amyloidosis and second-degree AV block type II, high-grade AV block or third-degree AV block, a permanent pacemaker is recommended.</b>	418,426,427, 445

AV block has been consistently linked to sudden death in patients with cardiac amyloidosis; for patients with obvious conduction system abnormalities, pacemaker implantation is recommended.

COR	LOE	Recommendations	References
<b>I</b>	<b>C-EO</b>	<b>In individuals with cardiac amyloidosis who have survived a cardiac arrest, an ICD is recommended if meaningful survival greater than 1 year is expected.</b>	

It is not known how many patients in the secondary prevention ICD trials had underlying cardiac amyloidosis. Nevertheless, there is agreement that patients who have been resuscitated following a cardiac arrest are at higher risk of recurrence and can potentially be revived by defibrillation.<sup>3</sup>

COR	LOE	Recommendations	References
<b>IIb</b>	<b>B-NR</b>	<b>In individuals with cardiac amyloidosis, the use of digoxin may be considered if used with caution due to the high risk of toxicity.</b>	446

Digoxin is known to bind to amyloid fibrils and putatively this action can potentiate its effect on the myocardium. In addition, many patients with cardiac amyloidosis have dysfunction related to the same disease process, and serum digoxin levels can be affected by the reduced excretion. In a cohort of 107 patients with AL amyloidosis who received digoxin, the incidence of significant arrhythmias due to digoxin toxicity was 11%, and 5 patients died.<sup>446</sup>

COR	LOE	Recommendations	References
<b>Iib</b>	<b>C-EO</b>	<b>In individuals with cardiac amyloidosis and symptomatic atrial arrhythmias, the use of sotalol, dofetilide, or amiodarone may be considered.</b>	

Although not studied in a retrospective or prospective manner, atrial arrhythmias are common, often highly symptomatic, and poorly tolerated, mostly due to rapid ventricular rates and irregular ventricular response that impair ventricular filling and contractility. Patients with significant ventricular diastolic disease can also present with symptomatic deterioration in the context of impaired filling without atrial systole, and antiarrhythmic agents are typically required. The class III antiarrhythmics (sotalol, dofetilide, and amiodarone) are mechanistically more suitable for therapy for this patient group, given the preponderance of atrial and ventricular myocardial fibrosis or scarring and the risk of atrial flutter and reentrant ventricular arrhythmia with class Ic agents. The use of class Ic agents can result in persistent atrial flutter in this patient group, which frequently exhibits substrate-related atrial tachycardias.

COR	LOE	Recommendations	References
<b>Iib</b>	<b>B-NR</b>	<b>In individuals with AL-type cardiac amyloidosis with nonsustained ventricular arrhythmias, a prophylactic ICD may be considered if meaningful survival greater than 1 year is expected.</b>	<sup>421</sup>

Primary prevention ICD implantation remains controversial, and there are conflicting data on the prevention of SCD in cardiac amyloidosis. Potentially curative therapies have emerged to manage certain subtypes,<sup>421</sup> and AL amyloidosis could be more favorable in this regard. Patients awaiting heart transplantation are also being considered for disease cure and should likely also be considered independently.

COR	LOE	Recommendations	References
<b>Iib</b>	<b>C-LD</b>	<b>In individuals with cardiac amyloidosis and symptomatic atrial arrhythmias, cardiac ablation may be considered.</b>	<sup>436</sup>

It is important for clinicians to recognize that ablation for atrial arrhythmias has limited efficacy and high recurrence rates, even when performed in major referral centers. Patients with rapid ventricular rates and those resistant to medical therapy also appear to benefit symptomatically from combined AV nodal ablation and permanent pacemaker implantation. In a cohort of 26 patients, 13 of whom underwent catheter ablation for atrial arrhythmia (atrial fibrillation, atrial flutter, or atrial tachycardia), the 1- and 3-year recurrence-free survival rate was 70% and 60%, respectively. The remaining 13 patients underwent AV node ablation. Both ablation groups had improved symptoms, and 11 patients died during the study period.<sup>436</sup>

## 5.2. Brugada syndrome

Since the initial clinical description of BrS, there has been a search for structural abnormalities in patients with the Brugada phenotype, which has been challenging to prove unequivocally. Simple imaging with transthoracic echocardiography is typically normal for patients with BrS, but the technique clearly lacks the ability to image this relevant heart region (ie, the RVOT area) with meaningful resolution. However, echocardiographic studies have demonstrated delayed activation of the RV, in which the degree of delay correlated well with the degree of ST-elevation.<sup>447</sup> However, higher-resolution CT and CMR have consistently revealed structural abnormalities and enlarged ventricular volumes,<sup>448,449</sup> which could be particularly relevant in patients with *SCN5A*-mediated BrS.<sup>450</sup> The potential contribution of structural abnormalities has taken on renewed interest with the advent of epicardial mapping and ablation<sup>451</sup> and recent preliminary histopathologic data from individuals with the Brugada phenotype and sudden death.<sup>452</sup>

Several groups have performed endomyocardial biopsies of patients with BrS, which have yielded mixed results, from findings of lymphocytic infiltrates to severe fibro-fatty infiltration suggestive of ARVC.<sup>453–455</sup> Frustaci et al examined 18 consecutive symptomatic patients with BrS

with endomyocardial biopsy of both ventricles, finding evidence of abnormalities in all patients.<sup>455</sup> Histopathology was subsequently shown to be heterogeneous in a subsequent study in 2008, whereby nonspecific lymphocytic changes in the biopsies of 21 patients with BrS could not be classified into any pathognomonic pattern.<sup>454</sup> In a recent evaluation of 6 postmortem hearts from presumed BrS-related sudden death, epicardial surface, interstitial fibrosis, and reduced GJ expression were observed in the RVOT.<sup>452</sup> Fibrosis and reduced GJ expression colocalized with abnormal potentials from previous epicardial mapping studies. These observations correlate with the previous observation that ablation of epicardial scar potentials attenuates and may even abolish the Brugada phenotype and life-threatening arrhythmias.<sup>451</sup> Abnormal myocardial structure and conduction are therefore likely to be at least partially responsible for the development of the Brugada phenotype.<sup>456</sup>

## 5.3. Potassium channels: KCNQ1, KCNH2, and TRMP4

### 5.3.1. *KCNQ1*

Xiong et al identified a 60-year-old man who initially presented with episodes of palpitations and was found to have recurrent VT with LBBB morphology on a 12-lead ECG,

frequent ventricular ectopy, and runs of NSVT on 24-hour Holter monitoring during the initial evaluation, with no family history of SCD, cardiac arrhythmias, or HF.<sup>457</sup> An echocardiogram showed an enlarged LV with mildly depressed LV systolic function with an ejection fraction of 45%. He had no obstructive coronary lesions on coronary angiography and subsequently underwent radiofrequency catheter ablation of the VT and ICD implantation and was administered a beta-blocker. Follow-up echocardiograms showed persistent LV dilation and systolic dysfunction and an LVEF of 42%. A *KCNQ1* p.R397Q pathologic variant, which was predicted to be disease-related, was identified at the C-terminal domain of the KCNQ1 channel protein. The *KCNQ1*-R397Q variant was located in the C-terminal domain of the  $\alpha$ -subunit of the functional KCNQ1 channel complex, which is considered an interacting domain necessary for the assembly of the channels at the membrane.<sup>458</sup> Tail current density and peak tail current density at +70 mV were significantly reduced in cells expressing the mutant protein, and localization of the mutant KCNQ1-R397Q protein to the cell membrane was reduced as compared with the KCNQ1-WT protein, all consistent with loss of function of KCNQ1. Loss-of-function variants in the *KCNQ1* gene are known to cause LQTS type 1 (LQT1), whereas a gain-of-function variant causes sinus bradycardia, familial atrial fibrillation, SQTS, and sudden infant death syndrome.<sup>459–463</sup> A 12-lead ECG in the index case with the *KCNQ1*-R397Q pathogenic variant showed a QTc interval of 480 ms in the presence of a severe intraventricular conduction defect. The clinical phenotype, which is distinct from the classic LQT1, is consistent with the loss-of-function effect of the *KCNQ1*-R397Q variant on trafficking of the KCNQ1 protein to the membrane and decreased  $I_{Ks}$  tail current density. The *KCNQ1*-R397Q variant was also identified in a 21-year-old female victim of SCD, whose cardiac autopsy demonstrated myocyte hypertrophy, disarray, fibrosis, and fatty replacement, a phenotype reminiscent of ACM.<sup>464</sup>

In addition, Kharbanda et al presented genetic and phenotypic data from 4 family members across 2 generations with evidence of prolonged QT interval and LVNC in association with a pathogenic variant in *KCNQ1*.<sup>465</sup> The association of LQTS LVNC is uncommon, with only 1 reported case in association with a pathogenic *KCNQ1* variant. In this case, a 5-year-old girl suffered a cardiac arrest and was found to have LVNC and prolonged QTc, and a previously reported pathogenic *KCNQ1* variant (c.1831G > T, D611Y), located in the C-terminus of *KCNQ1*. Several members of her family were found to carry this variant, but none had detected ECG or echocardiographic abnormalities.<sup>466</sup>

### 5.3.2. *KCNH2*

Two cases of LQTS and LVNC have also been reported by Ogawa et al, with both patients having different *KCNH2* variants.<sup>467</sup> SCD has occurred in these types of patients but has not been commonly reported. The optimal therapy is unclear

at this time, although beta-blocker therapy has been successful in treating *KCNQ1*- and *KCNH2*-associated LQTS. ICD implantation has been used for patients with this form of LQTS who experienced an episode of sudden cardiac arrest.<sup>465</sup>

### 5.3.3. *TRPM4*

The transient receptor potential melastatin 4 (TRPM4) channel mediates a  $Ca^{2+}$ -activated nonselective cationic current ( $I_{NSCa}$ ).<sup>468–470</sup> In the heart, the TRPM4 channel represents the cardiac  $Ca^{2+}$ -activated transient inward current ( $I_{ti}$ ) and plays a key role in the cardiac conduction system. At negative membrane potentials, TRPM4 channels catalyze  $Na^{+}$  entry into the cell, leading to cellular membrane depolarization. At positive membrane potentials, TRPM4 channels can catalyze cellular  $K^{+}$  efflux, leading to membrane repolarization. TRPM4 activity can therefore reduce or increase the driving force for  $Ca^{2+}$ . The potential influence of TRPM4 on the driving force of  $Ca^{2+}$  has an important impact on the frequency of intracellular  $Ca^{2+}$  oscillation in T-cells<sup>471</sup> and HLI-mouse cardiomyocytes.<sup>472</sup> Inhibition of TRPM4 channels in these cells abolishes the  $Ca^{2+}$  oscillations and leads to a phasic concentration of intracellular  $Ca^{2+}$ . TRPM4 is expressed in many cell types but is expressed most abundantly in the heart,<sup>468</sup> where it may participate in intracellular  $Ca^{2+}$  sensing and affect cellular excitability by influencing the membrane potential in all cell types. The impact of TRPM4 downregulation or upregulation depends on cell type and the presence of other ion channels, as well as exchangers and transporters.

Dominantly inherited variants in the TRPM4 gene of 4 families were shown to be associated with the cardiac bundle-branch disorder progressive familial heart block type I (PFHB1), isolated cardiac conduction disease (ICCD),<sup>473,474</sup> AV conduction block, RBBB, bradycardia, and BrS.<sup>475,476</sup>

TRPM4 channels carrying PFHB1 and ICCD variants display a dominant gain-of-function phenotype, which is not associated with alterations in biophysical properties but with an increase in TRPM4 current density.<sup>473,474</sup>

Daumy et al<sup>477</sup> reported on the genetic screening of 95 unrelated patients with progressive conduction system disease and identified 13 individuals with pathologic variants in the TRPM4 gene. One variant was found in a 4-generational family; systematic familial screening showed that there were 96 family members, 57 of whom could be recruited and studied. Twelve patients were diagnosed with conduction defects, 6 of whom (50%) underwent pacemaker implantation. Ten of the 12 patients presented with RBBB, 8 of whom showed left anterior hemiblock. Functional and biochemical analyses demonstrated that this variant, TRPM4-p.I376T, results in increased current density concomitant with augmented TRPM4 channel expression at the cell surface. LVNC was also identified in one of the family members. The affected patients were  $34 \pm 25$  years of age; however, babies, children, and adolescents were affected



as well. Almost no information regarding the patient with LVNC was provided, except that she had been diagnosed as a baby with LVNC, RBBB, and left anterior hemiblock, and had been implanted a pacemaker.

Using a custom gene panel consisting of 115 genes known to be associated with cardiomyopathic phenotypes and channelopathies, Forleo et al<sup>478</sup> analyzed 38 unrelated patients: 16 with DCM, 14 with HCM, and 8 with ARVC, recruited on the basis of more severe phenotypes and a family history of cardiomyopathy and/or sudden death. In 23 of 38 patients, at least one novel potential gene–phenotype association was identified. In the case of ACM, the authors found 1 patient with asymptomatic DCM and a *N915D-TRPM4* pathologic variant with a family history of sudden death in 3 of 4 affected family members. The authors also identified an *E289K-TRPM4* pathologic variant in a patient who presented with resuscitated cardiac arrest due to VF, an initial ECG with inverted T waves from V<sub>1</sub> to V<sub>3</sub>, and subsequent features of first-degree AV block, NSVT, paroxysmal atrial fibrillation, a 2D echocardiogram demonstrating a dilated RV, and a CMR that demonstrated dyskinetic areas at the free and inferior walls of the RV. The patient underwent ICD implantation. A *V1185I-TRPM4* pathologic variant was identified in the patient, who also had a family history of sudden death occurring in 3 of 4 affected family members. Therapy in this patient cohort included pacemaker implantation and, in some cases, an ICD.<sup>477</sup>

Saito et al also identified a *TRPM4* pathogenic variant in patients with ventricular noncompaction and cardiac conduction disease, thereby further expanding the role of *TRPM4* abnormalities in ACM.<sup>479</sup>

Management of cardiomyopathy also needs to be taken into account, using standard therapy.

#### 5.4. Phospholamban

Phospholamban, which is encoded by the *PLN* gene, is a transmembrane phosphoprotein of SR and is a key regulator of calcium homeostasis.<sup>129,480</sup> Pathogenic gene variants in *PLN*, mostly leading to the inhibition of calcium uptake into the SR, can cause genetic forms of cardiomyopathy, particularly those associated with early-onset of rhythm disturbance.<sup>480,481</sup> The pathogenic *PLN R14del* gene variant is commonly identified in patients diagnosed with ACM who have been initially diagnosed with DCM or ARVC.<sup>481,482</sup> In the Netherlands, the *PLN R14del* pathologic variant is a founder variant and has been identified in 10%–15% of patients diagnosed with ACM, either arrhythmogenic DCM or ARVC.<sup>33,483</sup> The phenotype of *PLN R14del* variant carriers, obtained from a limited number of index patients and family members, is characterized by a low-voltage ECG, a high frequency of malignant ventricular arrhythmias, and end-stage HF.<sup>33,481,482</sup> Natural history insights into this inherited disorder, including onset, risk stratification for malignant ventricular arrhythmias, mortality, and prevention of SCD, which require large, unselected multicenter cohorts consisting of index patients and relatives, are difficult to

identify; however, a number of studies have attempted to do so.<sup>80,161</sup> The yield from screening cardiomyopathy populations for pathologic *PLN* variants is generally very low, ranging from 0.08%–0.38% in selected cohorts.<sup>481,484</sup> The *PLN R14del* pathogenic variant was identified in 13% (31 of 240) of Dutch patients diagnosed with DCM and in 12% (12 of 97) of Dutch patients diagnosed with ARVC.<sup>33</sup> The arrhythmogenic burden of the *PLN R14del* pathogenic variant was demonstrated by the high rate of appropriate ICD discharges and a positive family history of SCD. Additionally, *PLN R14del* pathogenic variant carriers more frequently underwent cardiac transplantation compared with patients with familial DCM.<sup>33</sup> Cascade screening has identified many family members carrying the same pathogenic variants. Variable expression and age-dependent penetrance are characteristics observed with the *PLN R14del* pathogenic variant. Sepéhrkhoy et al evaluated the distribution pattern of cardiac fibrosis in hearts with desmosomal vs *PLN R14del* pathogenic variant cardiomyopathy and compared this pattern with fibrosis in other hereditary cardiomyopathies,<sup>485</sup> demonstrating that cardiomyopathies associated with desmosomal or the *PLN R14del* pathogenic variant have a distinct fibrosis pattern. The posterolateral wall of the LV was particularly discriminating, and hearts with the *PLN R14del* pathogenic variant cardiomyopathy showed significantly more fibrosis in the LV free wall than those with pathogenic desmosomal variants. Both desmosomal and *PLN R14del* pathogenic variants were strongly associated with life-threatening ventricular arrhythmias. Patients with pathogenic desmosomal variants had RV fibro-fatty changes and fibrosis with fatty changes in the outer part of the LV wall, predominantly in the posterolateral part, in line with earlier observations in autopsy studies from patients with ACM with unknown genotypes<sup>486</sup> and in transgenic mouse models of desmosomal ARVC.<sup>487</sup> LV pathology confirmed the LGE studies of CMR that typically involve the subepicardial and midwall layers of the inferolateral region of the LV in ACM.<sup>488–490</sup> Hearts from patients with a *PLN R14del* pathogenic variant also had a pattern of RV fibro-fatty replacement and LV fibrosis with fatty changes mostly in the posterolateral wall, regardless of clinical presentation.<sup>491,492</sup> However, hearts with the *PLN R14del* pathogenic variants had significantly more fibrosis in the LV and less fat in the RV compared with hearts with desmosomal variants. Recent observations were also confirmed from a cohort of 153 Dutch patients with ACM and in a combined United States and Dutch cohort of 577 patients in which more LV involvement in patients with *PLN* pathogenic variants was observed than in those with desmosomal pathogenic variants using electrocardiographic and imaging criteria (echocardiography, CMR, RV/LV cine-angiography).<sup>141,493</sup> The distribution in fibrosis patterns suggested that different variants could make the cardiomyocyte vulnerable to different stressors with potential damaging mechanisms that are not evenly distributed over the various regions of the myocardium. The authors speculated that the pattern of predominantly RV and

LV (posterolateral) epicardial fibrosis or fibrofatty replacement is induced by increased sensitivity to wall stress on the heart. This is supported by the demonstration that exercise induces a 125% increase in end-systolic wall stress in the RV, compared with only 14% in the LV,<sup>494</sup> suggesting that the RV is more vulnerable to wall stress.

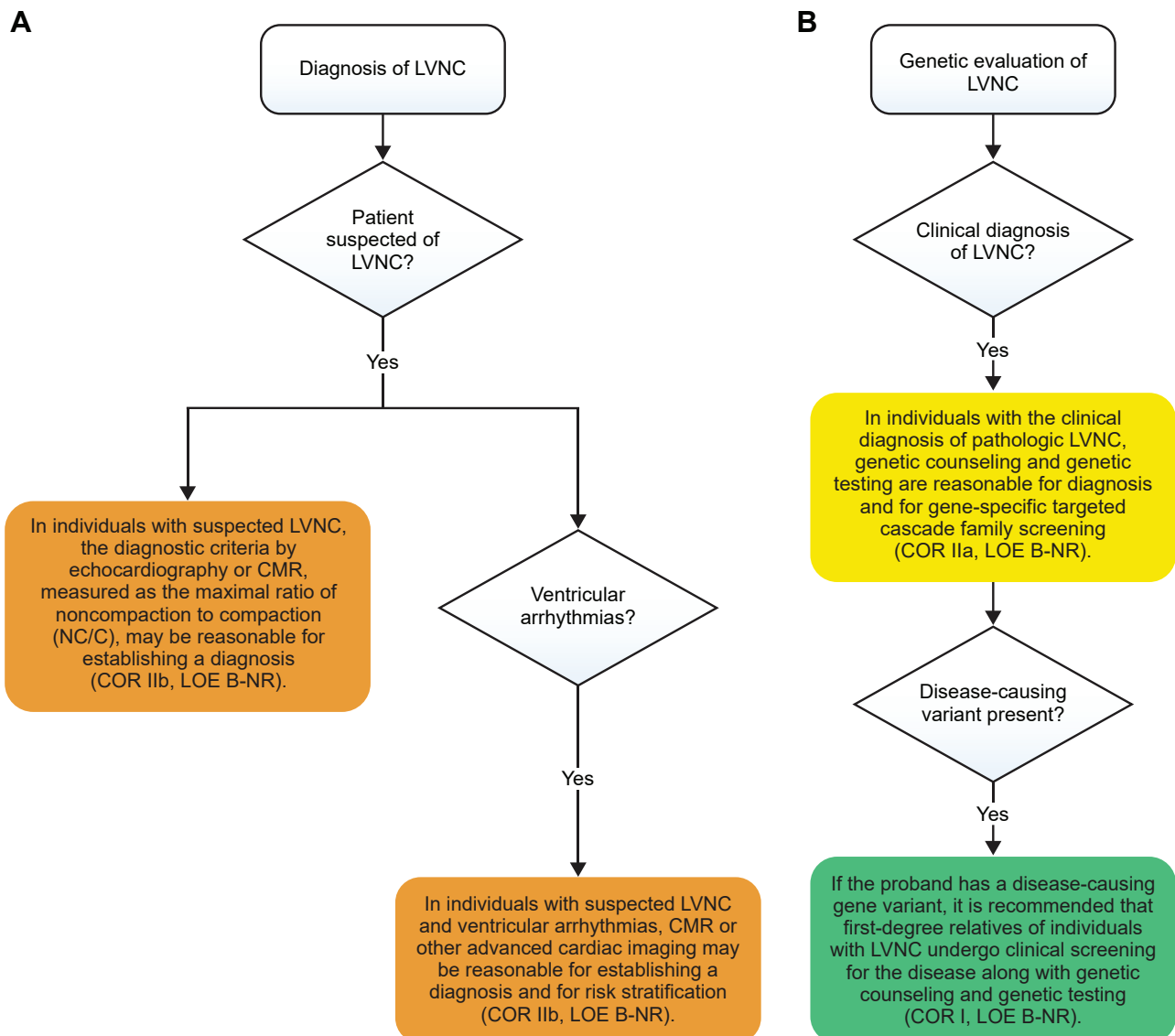
Following the arrhythmogenic profile of the *PLN R14del* pathogenic variant, primary prevention by implanting an ICD could be beneficial for variant carriers.<sup>33,481,482</sup>

### 5.5. Left ventricular noncompaction

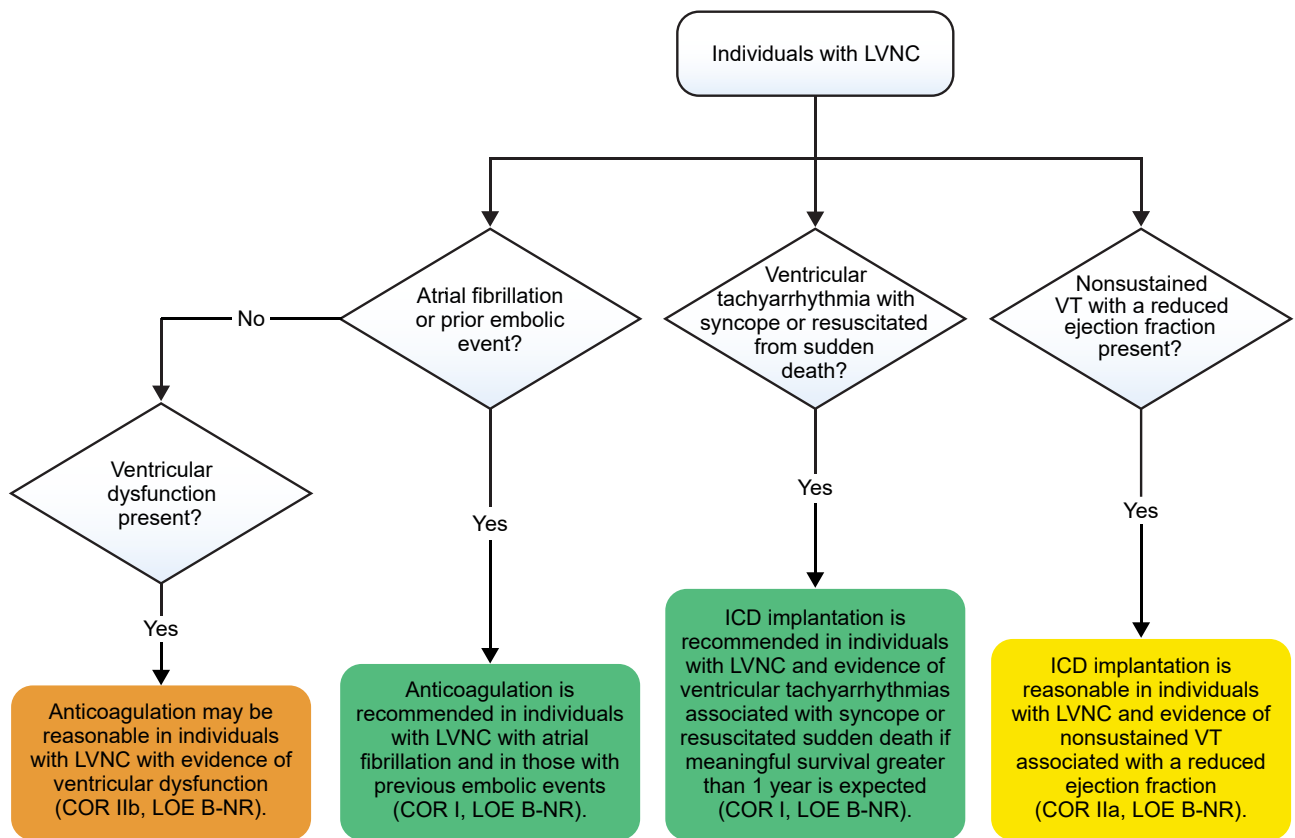
See Evidence Table: Left Ventricular Noncompaction. Recommendation flow diagrams are shown in [Figure 20](#) and [Figure 21](#).

LVNC is a genetic disorder characterized by excessive and unusual trabeculations within the LV, which is thought to occur due to developmental arrest and failure of the heart

to fully form the compact myocardium during the final phase of cardiac development.<sup>288,495</sup> Genetic inheritance arises in at least 30%–50% of patients and is thought to occur at a rate of approximately 1 case per 7000 live births.<sup>496,497</sup> LVNC is characterized by a spongy morphological appearance of the myocardium occurring primarily in the LV, with abnormal trabeculations typically being most evident in the apical, mid-lateral, and inferior portions of the LV.<sup>498–500</sup> The RV can also be affected, causing RV noncompaction or biventricular noncompaction.<sup>499,501</sup> The LV myocardium comprises 2 distinct layers, a compact and a noncompact layer, along with prominent trabeculae and deep intertrabecular recesses.<sup>495,497</sup> Apical thinning of the compact layer is also typical. These features may be associated with normal ventricular chamber dimensions, wall thickness and function, LV dilation or hypertrophy, systolic and/or diastolic dysfunction, atrial enlargement,



**Figure 20** Diagnosis and risk stratification of left ventricular noncompaction (LVNC) (A) and family and genetic evaluation of LVNC (B). CMR = cardiac magnetic resonance imaging; COR = Class of Recommendation; LOE = Level of Evidence; NC/C = maximum noncompaction to compaction ratio. Colors correspond to COR in [Figure 1](#).



**Figure 21** Left ventricular noncompaction (LVNC) treatment recommendations. Anticoagulation refers to vitamin K antagonists and direct oral anticoagulants. Children are often administered aspirin. COR = Class of Recommendation; ICD = implantable cardioverter defibrillator; LOE = Level of Evidence; VT = ventricular tachycardia. Colors correspond to COR in Figure 1.

various forms of congenital heart disease, or arrhythmias. Noncompaction cardiomyopathy is therefore phenotypically heterogeneous and can be subclassified into 9 different forms, including the most benign form (in which the LV size, thickness, and systolic and diastolic function are normal, with no associated early-onset arrhythmias), an RV form, a biventricular form, a DCM form, an HCM form, an RCM form, a mixed form (combination of HCM and DCM or DCM and RCM), a congenital heart disease form, and an arrhythmogenic form.<sup>11,499</sup> The more severe phenotypes are most typically observed in children, especially those younger than 1 year of age. High-resolution cardiac imaging, such as with CMR, has improved the ability to find the most benign form. Focal LVNC was observed in at least 1 LV myocardial segment in 43% of participants without heart disease or hypertension in a United States population-based CMR study and in 2 segments in 6% of this cohort.<sup>502</sup> These findings were replicated in a CMR study from a population cohort from the United Kingdom, in which 14.8% of individuals met at least 1 criterion for LVNC, and 4.4% met the most specific criterion.<sup>503</sup> The myocardium in LVNC can change

unexpectedly from one form to another (“undulating phenotype”).<sup>504</sup> Although many patients are asymptomatic, LV or RV failure commonly occurs and causes HF symptoms, which can be exercise-induced or persistent at rest. Patients undergoing long-term treatment sometimes present acutely with decompensated HF. Other life-threatening risks include ventricular arrhythmias and AV block, which can present clinically as syncope or sudden death.<sup>499</sup> Typically, rhythm abnormalities occur early in the presentation in some patients, most commonly being observed at the time of the initial diagnosis, consistent with an ACM. LVNC occurs in newborns, young children, adolescents, and adults, with the worst reported outcomes observed in infants and in those in the third and fourth decades of life. In some families, a consistent LVNC phenotype is observed in affected relatives; quite commonly, however, individuals with features of LVNC are found in families in which other affected relatives have been diagnosed with typical HCM, DCM, RCM, or ACM. Variants in approximately 15 genes have been implicated as causing noncompaction cardiomyopathy and include genes encoding desmosomal (desmoplakin and plakophilin 2), cytoskeletal, sarcomeric (most common),

and ion channel proteins. Disrupted mitochondrial function and metabolic abnormalities also have a causal role.<sup>353,354,505–508</sup> Treatment focuses on improving cardiac efficiency and reducing mechanical stress in those patients with systolic dysfunction. Arrhythmia therapy and ICD implantation to prevent sudden death are the mainstays of treatment when deemed necessary and appropriate.<sup>509</sup> LVNC can be associated with a malignant course in children or adults, and risk stratification is lacking.<sup>499,505,510</sup> Patients with LVNC associated with arrhythmias with or without systolic or diastolic dysfunction should avoid endurance exercise and competitive sports.

### 5.5.1. Diagnostic methods and criteria

#### 5.5.1.1. Noninvasive imaging

Echocardiography has been the diagnostic imaging technique of first choice, with CMR more recently becoming the diagnostic gold standard. The typical diagnostic criteria for echocardiography and CMR rely mainly on the ratio of the noncompacted layer to the compact layer thickness, evidence of intertrabecular recesses filled from the LV cavity by color Doppler echocardiography, and segmental localization of hypertrabeculation diagnostic of noncompaction. The ability of CMR to identify the presence and extent of LGE as a surrogate marker of myocardial fibrosis is also employed to determine the extent of LV scarring (which has been significantly related to ECG abnormalities and tachyarrhythmias) and LV dysfunction. In patients with LVNC evaluated by CMR, the degree of LV trabeculation had no prognostic effect over and above LV dilation, LV systolic dysfunction, and the presence of LGE.<sup>511</sup>

#### 5.5.1.2. Electrocardiography

Normal electrocardiographic results are rare in LVNC, with 80%–90% of ECGs being abnormal. Infants and young children commonly have excessive voltage, predominantly in the anterolateral leads.<sup>512</sup> These individuals, particularly those with early childhood presentation of LVNC, may have associated pre-excitation as well. Arrhythmias (including supraventricular tachycardia, VT, and atrial fibrillation/flutter) are common and dangerous accompaniments in LVNC. Conduction system abnormalities also occur. In the systematic review by Bhatia et al,<sup>513</sup> most arrhythmias in patients with LVNC were VT and atrial fibrillation, with the prevalence of VT approaching 40% and SCD resulting in more than 55% of LVNC-related deaths. Brescia et al<sup>510</sup> reported on the evaluation of 242 children with isolated LVNC and noted that 31 (12.8%) died, 150 (62%) presented with or developed cardiac dysfunction, and 13 (5.4%) underwent transplantation. The presence of cardiac dysfunction was strongly associated with mortality (HR: 11;  $P < .001$ ). ECG abnormalities were observed in 87% of the patients,

with ventricular hypertrophy and repolarization abnormalities occurring most commonly. Repolarization abnormalities were associated with increased mortality (HR: 2.1;  $P = .02$ ). Eighty (33.1%) children had an arrhythmia, and those with arrhythmias had increased mortality (HR: 2.8;  $P = .002$ ), with 42 (17.4%) having VT and 5 presenting with resuscitated SCD. In total, there were 15 cases of SCD in the cohort (6.2%). Nearly all patients who suddenly died (14 of 15) had abnormal cardiac dimensions or cardiac dysfunction and early-onset arrhythmias. The authors concluded that the mortality rate in children with LVNC has a strong association with arrhythmia development, with preceding cardiac dysfunction or ventricular arrhythmias associated with increased mortality. Muser et al studied 9 patients (mean age of  $42 \pm 15$  years) diagnosed with LVNC and ventricular arrhythmias, including 3 with VT and 6 with frequent PVCs despite treatment with a mean of  $2 \pm 1$  antiarrhythmic drugs.<sup>514</sup> The authors conducted EPSs and identified ablation sites using a combination of entrainment, activation, late or fractionated potential ablation, and pace mapping. Eight (89%) patients showed LV systolic dysfunction, with a mean ejection fraction of  $40\% \pm 13\%$ . Patients who presented with VT had evidence of abnormal electroanatomic substrate involving the mid to apical segments of the LV, which matched the noncompacted myocardial segments identified by CMR or echocardiography prior to the procedure. In patients presenting with frequent PVCs, the site of origin was identified at the papillary muscles (50%) and/or the basal septal regions (67%). After a median follow-up of 4 years (range 1–11) and a mean of  $1.8 \pm 1.1$  procedures, ventricular arrhythmias recurred in only 1 patient (11%), and significant improvement in LV function occurred in 50% of cases.

### 5.5.2. Treatment

According to the ACC/AHA guidelines on device-based therapy for cardiac rhythm abnormalities,<sup>4</sup> there are sufficient observational data to indicate that ICD placement as a strategy to reduce the risk of sudden death can be a reasonable clinical strategy for primary prevention for patients with LVNC.<sup>4</sup> ICD implantation should follow the general guidelines for primary and secondary prevention.<sup>4</sup> Patients with LVNC who have a moderate reduction in LV systolic function are more likely to have a primary prevention indication for ICD placement. Gleva et al evaluated 661 adults with LVNC, a mean age of  $46.4 \pm 14.9$  years (55% male, 45% female), 2/3 having HF (30% class III/IV) with a mean LVEF of  $33.4\% \pm 15.5\%$ . Atrial fibrillation/flutter occurred in 21% of patients, while 67% had nonsustained VT, and 30% had VT or prior VT arrest (5%).<sup>515</sup> In 78% of patients, an ICD was placed as primary prevention while 20% required an ICD for secondary prevention.

COR	LOE	Recommendations	References
<b>I</b>	<b>B-NR</b>	<b>If the proband has a disease-causing gene variant, it is recommended that first-degree relatives of individuals with LVNC undergo clinical screening for the disease along with genetic counseling and genetic testing.</b> <b>In individuals with the clinical diagnosis of pathologic LVNC, genetic counseling and genetic testing are reasonable for diagnosis and for gene-specific targeted cascade family screening.</b>	349,505,514
<b>IIa</b>	<b>B-NR</b>		349,505

LVNC is an autosomal dominant inherited disorder, which therefore has a 50% chance of being passed on from gene carriers to offspring or first-degree relatives. Genetic testing for individuals with LVNC could identify the causative gene and then allow for gene-specific targeted cascade family screening as a prevention measure that identifies at-risk family members. Variants in approximately 15 genes have been implicated as causative of noncompaction cardiomyopathy and include genes encoding desmosomal (desmoplakin and plakophilin 2), cytoskeletal, sarcomeric (most common), and ion channel proteins. In addition, disrupted mitochondrial function and metabolic abnormalities have a causal role.<sup>353,354,505-508</sup> In a study of 194 relatives of 50 unrelated LVNC probands,<sup>505</sup> 64% showed familial cardiomyopathy that also included HCM and DCM. Due to the substantial overlap of LVNC with other forms of cardiomyopathy, genetic testing panels should encompass genes in which variants are associated with these other forms of cardiomyopathy. Among 17 asymptomatic relatives, 8 carriers had nonpenetrance. In a study of 128 pediatric patients with LVNC,<sup>349</sup> 75 of whom underwent genetic testing, the yield was 9%. Furthermore, patients with isolated LVNC were less likely to have a genetic test. Given the genetic heterogeneity and variable presentation and penetrance of LVNC, family members need a comprehensive approach that includes clinical screening and genetic counseling and testing.

COR	LOE	Recommendations	References
<b>I</b>	<b>B-NR</b>	<b>ICD implantation is recommended in individuals with LVNC and evidence of ventricular tachyarrhythmias associated with syncope or resuscitated sudden death if meaningful survival greater than 1 year is expected.</b> <b>ICD implantation is reasonable in individuals with LVNC and evidence of nonsustained VT associated with a reduced ejection fraction.</b>	509
<b>IIa</b>	<b>B-NR</b>		509,510

Patients with LVNC with evidence of VT associated with syncope or resuscitated sudden death are at high risk. In a cohort of 44 prospectively analyzed patients with LVNC<sup>509</sup> who were implanted with an ICD for either secondary (n = 12 for VF or sustained VT) or primary (n = 32, for HF with severe LV dysfunction) prevention, 8 patients (4 implanted with an ICD for primary prevention and 4 implanted for secondary prevention) received appropriate ICD therapies in a median follow-up time of 6.1 months. Inappropriate ICD therapies occurred in 6 patients implanted with an ICD for primary prevention and in 3 patients implanted for secondary prevention. Complications with ICD implantation can occur regardless of the underlying etiology but are infrequent (estimated at less than 2% in a registry of patients that included those with LVNC).<sup>515</sup>

Among primary prevention patients, those who are at higher risk for adverse arrhythmic outcomes are associated with LV dysfunction. In a cohort of 242 pediatric patients with isolated LVNC,<sup>510</sup> 15 experienced SCD, 15 of whom had abnormal cardiac dimensions or ventricular function, whereas those children with normal function and dimensions were at low risk for sudden death. Of 42 patients with VT, 5 had presented with resuscitated SCD; the mortality risk was also increased for 80 children with an arrhythmia (HR: 2.8; P = .002).

COR	LOE	Recommendations	References
<b>I</b>	<b>B-NR</b>	<b>Anticoagulation is recommended in individuals with LVNC with atrial fibrillation and in those with previous embolic events.</b> <b>Anticoagulation may be reasonable in individuals with LVNC with evidence of ventricular dysfunction.</b>	516
<b>IIb</b>	<b>B-NR</b>		516

LVNC has an increased risk of thromboembolism when associated with atrial fibrillation or in individuals with prior embolism. Thrombus formation may occur in the intertrabecular recesses of the LV, leading to the possibility of ejection to the coronary arteries, causing ischemia, or to the brain, resulting in a stroke. In a cohort of 144 patients with LVNC,<sup>516</sup> stroke or peripheral embolism occurred in 22 patients, with 14 identified as due to a cardioembolic cause. A cardioembolic cause for stroke was related to either the presence of atrial fibrillation or systolic dysfunction. This further strengthens the indications for anticoagulation based upon well-established studies of stroke risk in patients with atrial fibrillation.<sup>517</sup> In pediatric patients aspirin is often used.

COR	LOE	Recommendations	References
Iib	B-NR	<b>In individuals with suspected LVNC, the diagnostic criteria by echocardiography or CMR, measured as the maximal ratio of noncompaction to compaction (NC/C), may be reasonable for establishing a diagnosis.</b>	375,511,515, 518,519
Iib	B-NR	<b>In individuals with suspected LVNC and ventricular arrhythmias, CMR or other advanced cardiac imaging may be reasonable for establishing a diagnosis and for risk stratification.</b>	511,519,520

The maximum noncompaction to compaction ratio (NC/C) in the LV has been employed as a diagnostic criterion with mixed results, and its relationship with outcomes is uncertain. In an analysis of 700 patients referred for CMR,<sup>519</sup> imaging criteria for LVNC were analyzed based on the ratio of noncompacted to compacted myocardium or trabeculation mass. The authors found a wide range for the apparent prevalence of LVNC according to the imaging criteria used and, furthermore, that the clinical outcome of death, ischemic stroke, VT, VF, or HF hospitalization was not related to the presence or absence of LVNC by any of the criteria. In a study of 199 patients with LV systolic dysfunction compared with healthy controls,<sup>375</sup> echocardiographic criteria for LVNC, including the ratio of noncompacted to compacted myocardium, were observed in 23.6% of the patients, with 5 control patients (4 of whom were black) meeting the echocardiographic criteria for LVNC despite having no history of cardiovascular disease. These findings raise into question the specificity of echocardiographic criteria to diagnose LVNC and suggest that trabeculation is the result of increased circulatory volume. This is further supported by a study of pregnant patients, which found that trabeculations are commonly observed during pregnancy, a time of increased LV loading conditions, and that trabeculations regress postpartum.<sup>518</sup>

For patients with suspected LVNC and ventricular arrhythmias, CMR or other advanced cardiac imaging can help establish a diagnosis and assist in risk stratification due to better visualization of areas of hypertrabeculation. In a study by Sidhu et al,<sup>520</sup> 8 patients with LVNC diagnosed by other methods (clinical, echocardiogram, and conventional magnetic resonance imaging [MRI]) underwent cardiac CT using a 17-segment model. Other patient groups studied included those with nonischemic DCM, severe aortic stenosis, severe aortic regurgitation, HCM, and LV hypertrophy due to hypertension and a control group of 20 patients without cardiovascular disease. The authors found that a ratio of noncompacted to compacted myocardium >2.3 distinguished LVNC, with a sensitivity of 88% and specificity of 97%.

In a study of 113 patients<sup>511</sup> with LVNC determined by echocardiography who underwent CMR, all demonstrated a ratio of noncompacted to compacted myocardium of at least 2.3 in diastole. Additional CMR criteria were analyzed, including LV dilation, LGE, and percentage of noncompacted myocardial mass (the ratio of noncompacted to compacted mass exceeding 3:1 or 2:1 based upon the segment that was analyzed). Patients were followed for cardiac events for a mean period of  $48 \pm 24$  months. LV dilation, systolic dysfunction, and fibrosis were found to be predictors of cardiac events but not the indices related to noncompacted myocardium. The use of advanced cardiac imaging in patients suspected of LVNC can help establish the diagnosis and possibly provide risk stratification.

The data published in the Multi-Ethnic Study of Atherosclerosis suggest that, using CMR, a ratio of trabeculated to compact myocardium of >2.3 is common in a large population-based cohort (43% had a ratio >2.3 in at least 1 region). Only 6% of participants in the study had a maximum ratio >2.3 in more than 2 regions in an older age population (mean age of 68 years).<sup>502,521</sup>

See Table 5 for diagnostic criteria for LVNC.

## Section 6 Future directions and research recommendations

In the future, a variety of new approaches to the understanding of mechanisms responsible for the development and progression of ACMs will be a key focus. With this knowledge, novel treatment options based on targeting members of final common pathways at the gene and protein level can potentially be designed and tested. Gene editing could also provide novel options, as could regeneration medicine. To achieve

these goals, research must focus on the array of disorders categorized under the umbrella of ACMs. Potential topics for study would include the following:

1. Mechanisms of desmosome/ID disruption and cell–cell pulling apart.
2. Mechanisms by which exercise results in early-onset and increased severity of ACM.
3. Mechanisms responsible for generating arrhythmias.
4. Nondesmosomal causes of ACM.

**Table 5 Diagnostic criteria for left ventricular noncompaction (LVNC)**

References	Modality	N	LVNC diagnostic criteria
522	Echo	8	2 layers, excessively prominent ventricular trabeculations, progressively increased total myocardial wall thickness from mitral valve and toward the apex, $CM/(NCM + CM) \leq 0.5$ at end-diastole (short-axis parasternal and/or apical views)
523	Echo	34	2 layers, intertrabecular recesses by CFD, no co-existing structural abnormality, $NC/C$ layer $\geq 2$
373	Echo	62	>3 trabeculations protruding from LV wall apically to papillary muscle. End-diastolic $NC/C$ layer $\geq 2$
497	MRI	7	2 layers. End-diastolic $NC/C > 2.3$
524	MRI	16	Total LV trabeculated mass without papillary muscles. End-diastolic NC layer volume >20%

C = compaction; CM = compacted myocardium; echo = echocardiogram; LV = left ventricular; MRI = magnetic resonance imaging; NC/C = maximum noncompaction to compaction ratio; NCM = noncompacted myocardium.

5. Utility of genetic testing in ACM prognosis.
6. Differences between right- and left-sided disease outcomes.
7. Medical therapy approaches.
8. Arrhythmia management approaches.
9. Gene editing and regenerative medicine; scientific methods and studies in animals and humans.

## Appendix.

### Supplementary Data

Supplementary data (Appendix 3) and interview video associated with this article can be found in the online version at <https://doi.org/10.1016/j.hrthm.2019.05.007>.

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N.A. Mark Estes, III, MD, FHRS, CCDS	University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania	1: Abbott; 1: Boston Scientific; 1: Medtronic	None	None	None	None	None	None	None	None
Wei Hua, MD, FHRS	Fu Wai Hospital, Beijing, China	None	None	None	None	None	None	None	None	None
Julia H. Indik, MD, PhD, FHRS	University of Arizona, Sarver Heart Center, Tucson, Arizona	None	None	None	None	None	None	None	None	2: ACC
Jodie Ingles, MPH, PhD, FHRS	Agnes Ginges Centre for Molecular Cardiology at Centenary Institute, The University of Sydney, Sydney, Australia	None	None	None	None	None	None	None	None	None
Cynthia A. James, ScM, PhD, CGC	Johns Hopkins University, Baltimore, Maryland	1: Abbott	None	1: NSGC; 2: Boston Scientific	None	None	None	None	None	0: NSGC
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Roberto Keegan, MD	Hospital Privado Del Sur, Buenos Aires, Argentina, and Hospital Español, Bahia Blanca, Argentina	None	None	None	None	None	None	None	None	None
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Mark S. Link, MD, FHRS	UT Southwestern Medical Center, Dallas, Texas	None	None	None	None	None	None	None	None	None
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Writing group member	Employment	Honoraria/ Speaking/ Consulting	Speakers' bureau	Research*	Fellowship support*	Ownership/ Partnership/ Principal/ Majority stockholder	Stock or stock options	Intellectual property/ Royalties	Other
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Shubhayan Sanatani, MD, FHRS, CCDS	Children's Heart Center, Vancouver, Canada	None	None	None	None	None	None	None	None
Wataru Shimizu, MD, PhD	Department of Cardiovascular Medicine, Nippon Medical School, Tokyo, Japan	None	None	None	None	None	None	None	None
J. Peter van Tintelen, MD, PhD	Utrecht University Medical Center Utrecht, University of Utrecht, Department of Genetics, Utrecht, the Netherlands; University of Amsterdam Academic Medical Center, Amsterdam, the Netherlands	None	None	None	None	None	None	None	None
Arthur A.M. Wilde, MD, PhD	University of Amsterdam, Academic Medical Center, Amsterdam, the Netherlands; Department of Medicine, Columbia University Irving Medical Center, New York, New York; European Reference Network for Rare and Low Prevalence Complex Diseases of the Heart	None	None	None	None	None	None	None	None

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Number value: **0** = \$0; **1** = ≤\$10,000; **2** = >\$10,000 to ≤\$25,000; **3** = >\$25,000 to ≤\$50,000; **4** = >\$50,000 to ≤\$100,000; **5** = >\$100,000.

ACC = American College of Cardiology; AHA = American Heart Association; NIH = National Institutes of Health; NSGC = National Society of Genetic Counselors.

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**Appendix 2 Peer reviewer disclosure table**

Peer reviewer	Employment	Honoraria/ Speaking/ Consulting	Speakers' bureau	Research*	Fellowship support*	Ownership/ Partnership/ Principal/ Majority stockholder	Stock or stock options	Intellectual property/ Royalties	Other
Peter Aziz, MD	Cleveland Clinic, Cleveland, Ohio	None	None	None	None	None	None	None	None
Mina K. Chung, MD, FHRS	Cleveland Clinic, Cleveland, Ohio	2: ABIM	None	5: AHA; 5: NIH	None	None		1: Elsevier; 1: UpToDate	0: ACC (EP Section Leadership Council member); 0: AHA (Chair, ECG & Arrhythmias Committee; Member, Clinical Cardiology Leadership Committee; Member, Committee on Scientific Sessions Programming); 0: Amarin (Data monitoring committee member); 0: BIOTRONIK; 2: AHA (Associate Editor, <i>Circulation Arrhythmia and Electrophysiology</i> )
Shriprasad Deshpande, MBBS, MS	Children's National, Washington, DC	None	None	None	None	None	None	None	None
Susan Etheridge, MD, FACC	University of Utah, Salt Lake City, Utah	1: UpToDate	None	0: NIH	None	None	None	None	0: Sudden Arrhythmia Death Foundation
Marcio Jansen de Oliveira Figueiredo, MD	University of Campinas, São Paulo, Brazil	1: Boehringer Ingelheim; 1: Daiichi-Sankyo	None	None	None	None	None	None	None
John Gorcsan III, MD, FASE	Washington University School of Medicine, St. Louis, Missouri	1: EBR systems; 1: V- wave, Inc.	None	2: V-wave Inc.; 2: EBR Systems	None	None	None	None	None
Denise Tessariol Hachul, MD	Heart Institute, University of São Paulo, São Paulo, Brazil	None	None	None	None	None	None	None	None
Robert Hamilton, MD	The Hospital for Sick Children, Toronto, Ontario	None	None	None	None	None	None	None	None

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Yuki Iwasaki, MD, PhD	Nippon Medical School, Tokyo, Japan	None	None	None	None	None	None	None	None
Rajesh Janardhanan, MD, MRCP, FACC, FASE	University of Arizona College of Medicine, Tucson, Arizona	None	None	None	None	None	None	None	None
Neal Lakdawala, MD	Brigham and Women's Hospital, Boston, Massachusetts	1: Array Biopharma; 1: MyoKardia	None	None	None	None	None	None	None
Andrew P. Landstrom, MD, PhD	Duke University School of Medicine, Durham, North Carolina	None	None	None	None	None	None	None	None
Andrew Martin, MBChB, CCDS	Green Lane Cardiovascular Service, Auckland, New Zealand	None	None	None	None	None	None	None	None
Ana Morales, MS	The Ohio State University, Columbus, Ohio	1: NSGC	None	4: NIH	None	None	None	None	None
Brittney Murray, MS	Johns Hopkins Hospital, Baltimore, Maryland	1: Clear Genetics; 1: My Gene Counsel; 1: PWN Health	None	None	None	None	None	None	None
Santiago Nava Townsend, MD	Departamento de Electrofisiología Cardiaca, Instituto Nacional de Cardiología Ignacio Chávez, Mexico City, Mexico	1: Cook Medical; 2: CORDIS-Johnson & Johnson	None	None	None	None	None	None	None
Stuart Dean Russell, MD	Duke University School of Medicine, Durham, North Carolina	1: Medtronic	None	0: Abbott Laboratories; 0: SubQ Pharmaceuticals	None	None	None	None	None
Frederic Sacher, MD, PhD	LIRYC Institute/ Bordeaux University, Pessac, France	1: Abbott Laboratories; 1: Bayer; 1: Biosense Webster; 1: Boehringer Ingelheim; 1: Boston Scientific; 1: LivaNova; 1: Medtronic; 1: Pfizer	None	None	None	None	None	None	None
Mauricio Scanavacca, MD	Instituto do Coração, São Paulo, Brazil	None	None	None	None	None	None	None	None

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Appendix 2 (Continued)

Peer reviewer	Employment	Honoraria/ Speaking/ Consulting	Speakers' bureau	Research*	Fellowship support*	Ownership/ Partnership/ Principal/ Majority stockholder	Stock or stock options	Intellectual property/ Royalties	Other
Kavita Sharma, MD	Johns Hopkins University, Baltimore, Maryland	1: Novartis Pharmaceuticals Corporation	None	3: NIH; 3: AHA	None	None	None	None	None
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Harikrishna Tandri, MBBS, MD	Johns Hopkins University, Baltimore, Maryland	1: Abbott	None	None	None	None	None	None	None
Gaurav A. Upadhyay, MD, FACC	University of Chicago Medicine, Chicago, Illinois	1: Abbott Laboratories; 1: BIOTRONIK; 1: CardioNet; 1: Medtronic; 1: ZOLL Medical Corporation	None	None	None	None	None	None	None
Christian Wolpert, MD	University Hospital Mannheim, Ludwigsburg, Germany	None	None	None	None	None	None	None	None

Number value: 0 = \$0; 1 = ≤\$10,000; 2 = >\$10,000 to ≤\$25,000; 3 = >\$25,000 to ≤\$50,000; 4 = >\$50,000 to ≤\$100,000; 5 = >\$100,000.

ABIM = American Board of Internal Medicine; ACC = American College of Cardiology; AHA = American Heart Association; NIH = National Institutes of Health; NSGC = National Society of Genetic Counselors.

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