2019 HRS expert consensus statement on evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy: Executive summary

Jeffrey A. Towbin, MS, MD (Chair)[1,2] William J. McKenna, MD, DSc (Vice-Chair)[3] Dominic J. Abrams, MD, MRCP, MBA,[4] Michael J. Ackerman, MD, PhD,[5,*] Hugh Calkins, MD, FHRS, CCDS,[6] Francisco C.C. Darrieux, MD, PhD,[7,†] James P. Daubert, MD, FHRS,[8] Christian de Chillou, MD, PhD,[9,‡] Eugene C. DePasquale, MD,[10,§] Milind Y. Desai, MD,[11,¶] N.A. Mark Estes III, MD, FHRS, CCDS,[12] Wei Hua, MD, FHRS,[13,#] Julia H. Indik, MD, PhD, FHRS,[14] Jodie Ingles, MPH, PhD, FHRS,[15,**] Cynthia A. James, ScM, PhD, CGC,[6] Roy M. John, MBBS, PhD, CCDS, FHRS,[16] Daniel P. Judge, MD,[17,††] Roberto Keegan, MD,[18,19,‡‡] Andrew D. Krahn, MD, FHRS,[20] Mark S. Link, MD, FHRS,[21,§§] Frank I. Marcus, MD,[14] Christopher J. McLeod, MBChB, PhD, FHRS,[5] Luisa Mestroni, MD,[22] Silvia G. Priori, MD, PhD,[23,24,25] Jeffrey E. Saffitz, MD, PhD,[26] Shubhayan Sanatani, MD, FHRS, CCDS,[27,¶¶] Wataru Shimizu, MD, PhD,[28,##] J. Peter van Tintelen, MD, PhD,[29,30] Arthur A.M. Wilde, MD, PhD,[24,29,31] Wojciech Zareba, MD, PhD[32]

Document Reviewers: Peter Aziz, MD; Mina K. Chung, MD, FHRS; Shriprasad Deshpande, MBBS, MS; Susan Etheridge, MD, FACC; Marcio Jansen de Oliveira Figueiredo, MD; John Gorcsan III, MD, FASE; Denise Tessariol Hachul, MD; Robert Hamilton, MD; Richard Hauer, MD; Minoru Horie, MD, PhD; Yuki Iwasaki, MD, PhD; Rajesh Janardhanan, MD, MRCP, FACC, FASE; Neal Lakdawala, MD; Andrew P. Landstrom, MD, PhD; Andrew Martin, MBChB, CCDS; Ana Morales, MS; Brittney Murray, MS; Santiago Nava Townsend, MD; Stuart Dean Russell, MD; Frederic Sacher, MD, PhD; Mauricio Scanavacca, MD; Kavita Sharma, MD; Yoshihide Takahashi, MD; Harikrishna Tandri, MBBS, MD; Gaurav A. Upadhyay, MD, FACC; Christian Wolpert, MD

From the [1]Le Bonheur Children's Hospital, Memphis, Tennessee, [2]University of Tennessee Health Science Center, Memphis, Tennessee, [3]University College London, Institute of Cardiovascular Science, London, United Kingdom, [4]Boston Children's Hospital, Boston, Massachusetts, [5]Mayo Clinic, Rochester, Minnesota, [6]Johns Hopkins University, Baltimore, Maryland, [7]Universidade de São Paulo, Instituto do Coração HCFMUSP, São Paulo, Brazil, [8]Duke University Medical Center, Durham, North Carolina, [9]Nancy University Hospital, Vandoeuvre-lès-Nancy, France, [10]University of California Los Angeles, Los Angeles, California, [11]Cleveland Clinic, Cleveland, Ohio, [12]University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, [13]Fu Wai Hospital, Beijing, China, [14]University of Arizona, Sarver Heart Center, Tucson, Arizona, [15]Agnes Ginges Centre for Molecular Cardiology at Centenary Institute, The University of Sydney, Sydney, Australia, [16]Vanderbilt University Medical Center, Nashville, Tennessee, [17]Medical University of South Carolina, Charleston, South Carolina, [18]Hospital Privado Del Sur, Buenos Aires, Argentina, [19]Hospital Español, Bahia Blanca, Argentina, [20]The University of British Columbia, Vancouver, Canada, [21]UT Southwestern Medical Center, Dallas, Texas, [22]University of Colorado Anschutz Medical Campus, Aurora, Colorado, [23]University of Pavia, Pavia,

 https://doi.org/10.1016/j.hrthm.2019.09.019

Italy, [24]*European Reference Network for Rare and Low Prevalence Complex Diseases of the Heart (ERN GUARD-Heart),* [25]*ICS Maugeri, IRCCS, Pavia, Italy,* [26]*Beth Israel Deaconess Medical Center, Boston, Massachusetts,* [27]*Children's Heart Center, Vancouver, Canada,* [28]*Department of Cardiovascular Medicine, Nippon Medical School, Tokyo, Japan,* [29]*University of Amsterdam, Academic Medical Center, Amsterdam, the Netherlands,* [30]*Utrecht University Medical Center Utrecht, University of Utrecht, Department of Genetics, Utrecht, the Netherlands,* [31]*Department of Medicine, Columbia University Irving Medical Center, New York, New York, and* [32]*University of Rochester Medical Center, Rochester, New York.*

**Representative of the American College of Cardiology (ACC)*
†Representative of the Sociedade Brasileira de Arritmias Cardíacas (SOBRAC)
‡Representative of the European Heart Rhythm Association (EHRA)
§Representative of the International Society for Heart & Lung Transplantation (ISHLT)
¶Representative of the American Society of Echocardiography (ASE)
#Representative of the Asia Pacific Heart Rhythm Society (APHRS)
***Representative of the National Society of Genetic Counselors (NSGC)*
††Representative of the Heart Failure Society of America (HFSA)
‡‡Representative of the Latin American Heart Rhythm Society (LAHRS)
§§Representative of the American Heart Association (AHA)
¶¶Representative of the Pediatric & Congenital Electrophysiology Society (PACES)
##Representative of the Japanese Heart Rhythm Society (JHRS)

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; **ALVC** = arrhythmogenic left ventricular cardiomyopathy; **ARB** = angiotensin receptor blocker; **ARVC** = arrhythmogenic right ventricular cardiomyopathy; **AV** = atrioventricular; **CMR** = cardiac magnetic resonance imaging; **COR** = Class of Recommendation; **DCM** = dilated cardiomyopathy; **ECG** = electrocardiogram; **EPS** = electrophysiology study; **ICD** = implantable cardioverter defibrillator; **LOE** = Level of Evidence; **LV** = left ventricle; **LVNC** = left ventricular noncompaction; **MET** = metabolic equivalent; **NSVT** = nonsustained ventricular tachycardia; **NYHA** = New York Heart Association; **PVC** = premature ventricular contraction; **RV** = right ventricle; **VF** = ventricular fibrillation; **VT** = ventricular tachycardia (Heart Rhythm 2019;16:e373–e407)

Developed in collaboration with and endorsed by the American College of Cardiology (ACC), the American Heart Association (AHA), the American Society of Echocardiography (ASE), the Asia Pacific Heart Rhythm Society (APHRS), 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). Correspondence: Heart Rhythm Society, 1325 G Street NW, Suite 400, Washington, DC 20005. E-mail address: clinicaldocs@hrsonline.org.

TABLE OF CONTENTS

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 3.7. A member of the

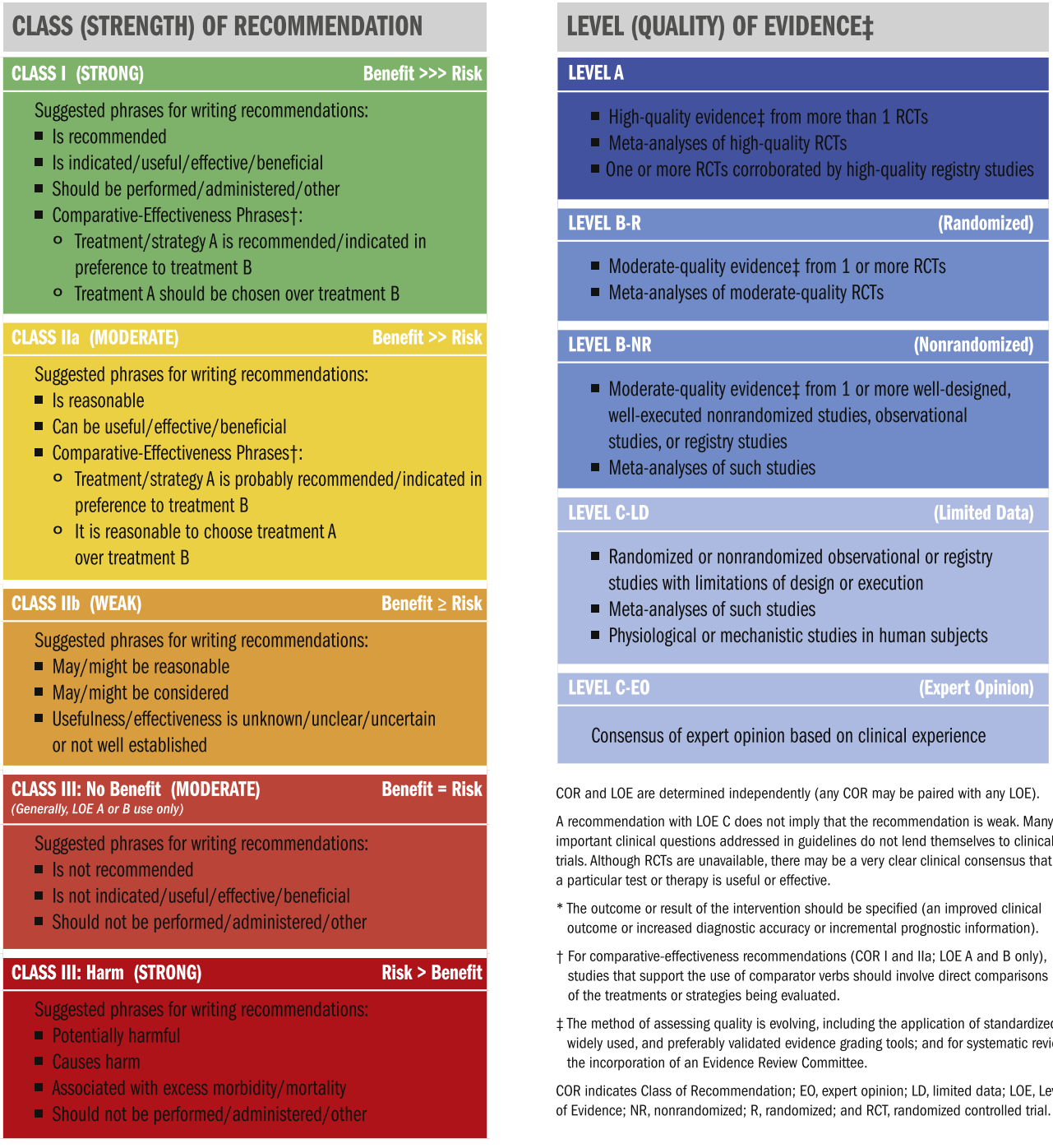

Figure 1 ACC/AHA Recommendation System: Applying Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, and Diagnostic Testing in Patient Care.* Reproduced with permission of the American College of Cardiology and the American Heart Association.[2]

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

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

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.[1] 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

ACM refers to an arrhythmogenic disorder of myocardium not secondary to ischemic, hypertensive, or valvular heart disease. In this expert consensus statement, ACM incorporates a broad spectrum of genetic, systemic, infectious, and inflammatory disorders. This designation includes, but is not limited to, arrhythmogenic right ventricular cardiomyopathy (ARVC), arrhythmogenic left ventricular cardiomyopathy (ALVC), ion channel abnormalities, amyloidosis, and left ventricular noncompaction (LVNC). The ACM phenotype overlaps with other cardiomyopathies, particularly dilated cardiomyopathy (DCM), with arrhythmia presentation accompanied by ventricular dilatation and/or impaired systolic function. ACM is a type of hereditary cardiovascular disease that demonstrates a "final common pathway" with genetic heterogeneity but similar phenotypes resulting from abnormalities in genes encoding proteins of similar function or genes encoding proteins participating in a common pathway cascade.

The top ten take-home messages based on novel concepts and Class I recommendations for ACM are as follows:

1) ACM is an inclusive designation referring to an arrhythmogenic disorder of myocardium characterized by a clinical presentation with documented and/or symptomatic arrhythmia as a distinguishing feature.
2) Genetic testing is indicated for all disease-associated genes and variants in patients and decedents.
3) Genetic counseling with a comprehensive 3-generation family history should be performed.
4) Clinical evaluation including electrocardiogram (ECG), cardiac imaging, and ambulatory monitoring is recommended for first-degree relatives every 1–3 years beginning at 10–12 years of age.
5) Implantable cardioverter defibrillator (ICD) placement for primary and secondary prevention of sudden cardiac death is recommended in individuals with ACM who have suffered a cardiac arrest with ventricular tachycardia (VT) or ventricular fibrillation (VF), in individuals with ACM who have sustained VT not hemodynamically tolerated, in individuals with ACM and LVEF 35% or lower and NYHA class II-III symptoms and an expected

meaningful survival of greater than 1 year, and in individuals with ACM not due to ARVC and hemodynamically tolerated VT.

6) A shared decision-making approach to ICD placement should be used.
7) Beta-blocker therapy should be used for sinus tachycardia, supraventricular arrhythmias, atrial fibrillation, or atrial flutter with ventricular rates resulting in ICD therapy.
8) For exercise with ARVC, 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.
9) For cardiac amyloidosis, symptomatic and asymptomatic individuals with cardiac amyloidosis and second-degree AV block type II, high-grade AV block or third-degree AV block, should receive a permanent pacemaker, and individuals with cardiac amyloidosis who have survived a cardiac arrest, should receive an ICD if meaningful survival greater than 1 year is expected.
10) In individuals with LVNC, if the proband has a disease-causing gene variant, it is recommended that first-degree relatives undergo clinical screening for the disease along with genetic counseling and genetic testing. ICD implantation is recommended in individuals with LVNC if there is evidence of ventricular tachyarrhythmias associated with syncope or resuscitated sudden death and if meaningful survival greater than 1 year is expected, and anticoagulation is recommended in individuals with LVNC if there is atrial fibrillation and/or previous embolic events.

This section discusses the features and presentation of ACM (Figure 2, Figure 3, and Figure 4), ARVC, ALVC, and the final common pathways in ACM (Figure 5 and Figure 18), where 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.

Section 2.1 Arrhythmogenic cardiomyopathy

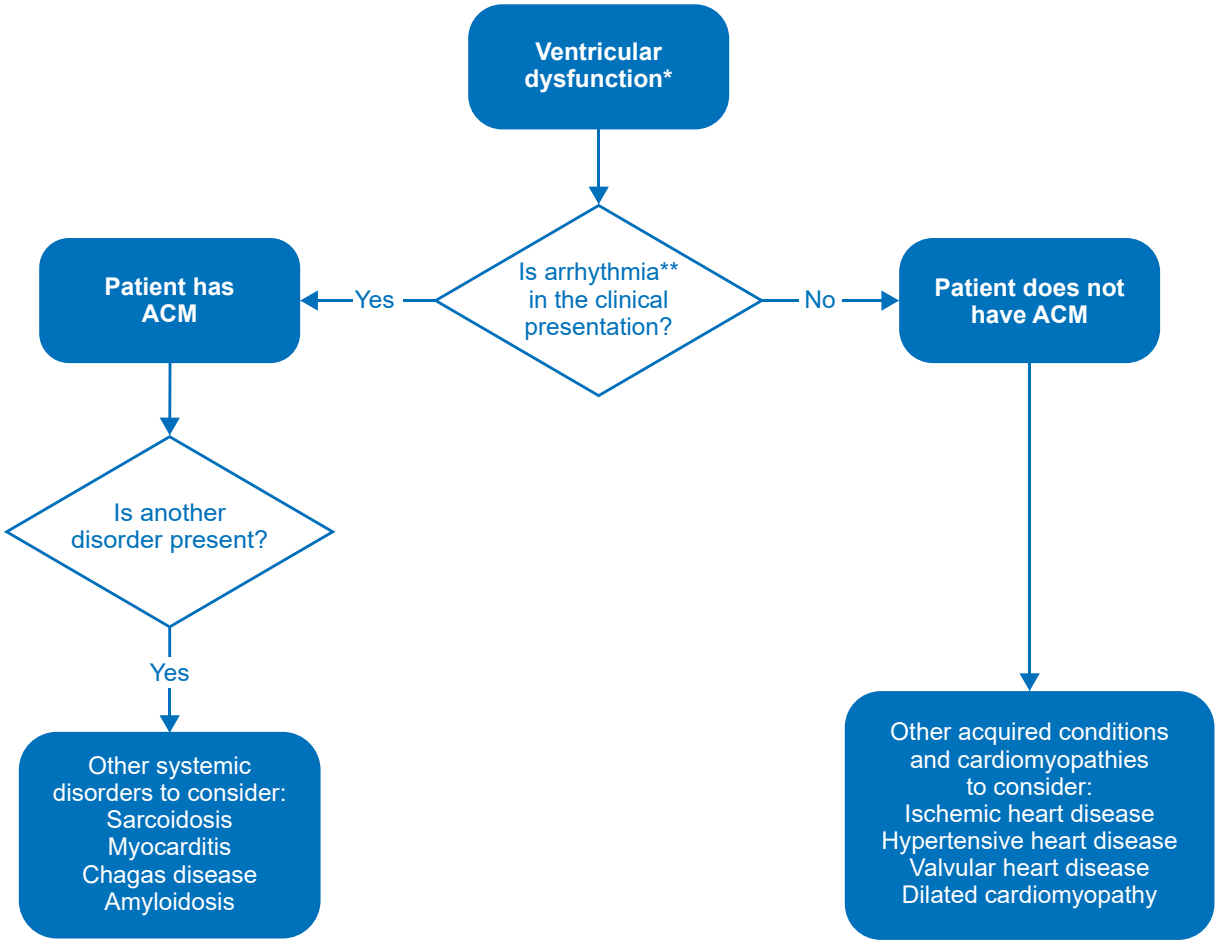

Figure 2 Algorithm to consider the presence of an arrhythmogenic cardiomyopathy (ACM).

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.

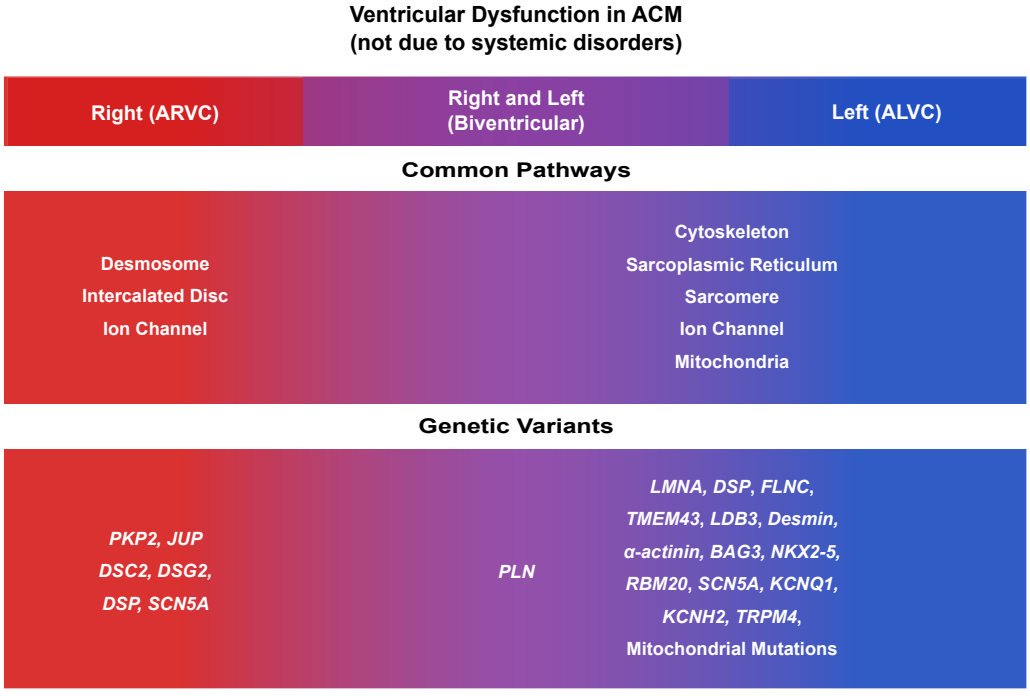

Figure 4 Approach to understanding the common pathway and genetic variants in a patient with arrhythmogenic cardiomyopathy (ACM) according to the predominant ventricular dysfunction. See also Table 3. ALVC = arrhythmogenic left ventricular cardiomyopathy; ARVC = arrhythmogenic right ventricular cardiomyopathy; *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.

Section 2.2 Final common pathways in arrhythmogenic cardiomyopathy

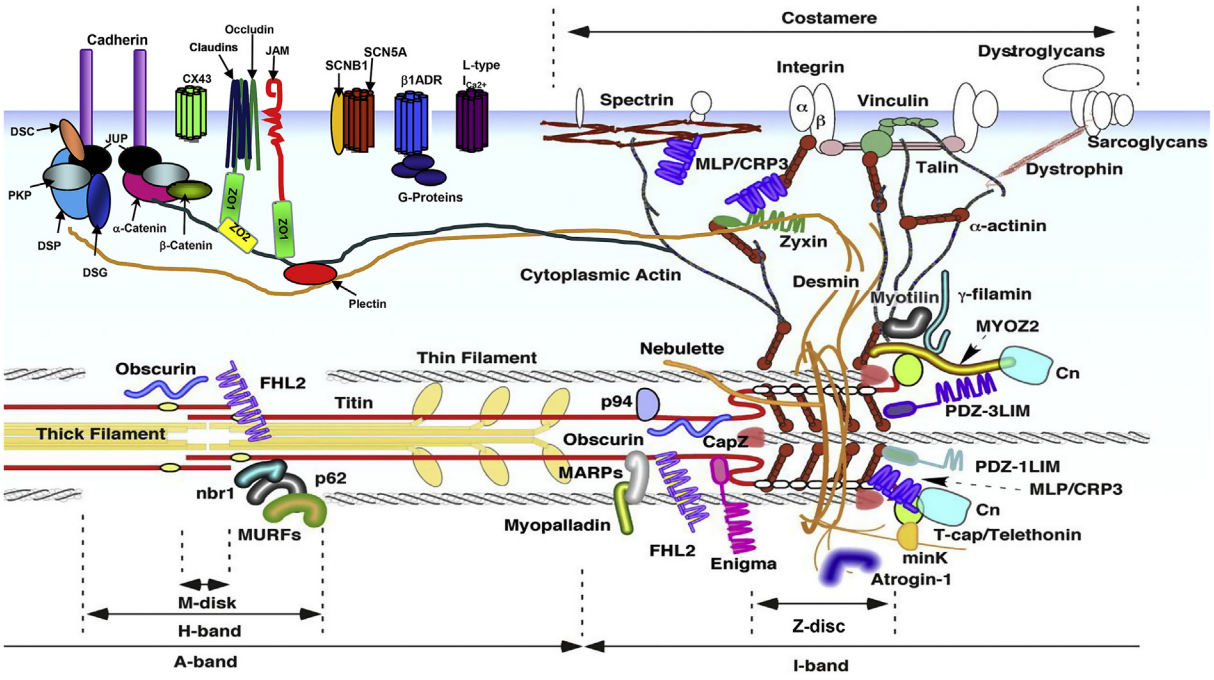

Figure 5 Cytoskeletal protein complexes within the cardiomyocyte costamere and Z-disc. Force is distributed externally from the costameres and internally throughout the myocyte by the Z-disc. Structural and signaling proteins within the costamere and Z-disc are shown. Many of these proteins have been 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; MAPRs = muscle ankyrin repeat proteins; MURFs = muscle-specific ring-finger proteins. Modified with permission of the American Physiological Society.[13]

Section 3 Diagnosis and treatment of arrhythmogenic cardiomyopathy

This section covers the diagnosis and evaluation of ACM. The modified Task Force Criteria for ARVC (Figure 6) is discussed. ECG features in ARVC including repolarization abnormalities (Figure 7), depolarization and conduction abnormalities of epsilon wave and prolonged terminal activation duration (Figure 8), ECG abnormalities in ACM other than ARVC, ambulatory ECG monitoring, and signal-averaged ECG. Cardiac imaging, electrophysiology testing, and endomyocardial biopsy to diagnose ACM are also covered. Genetic testing for the diagnosis and management of ARVC and other ACMs is discussed in detail including variant and gene interpretation (Table 2), choice of genetic test (Table 3), advantages and disadvantages of various methods for screening genes (Table 4), recommendations for who to study, and the role of genetic testing in ACM. Within genetic testing, the use of genetic testing for ACM risk stratification and management includes the topics of left ventricular (LV) dysfunction, multiple variants, and the specific genes and variants for which there is evidence for a clinically actionable relationship between genotype and phenotype. The specific genes and variants covered are desmosomal genes (Figure 9), lamin A/C (*LMNA*), desmoplakin (*DSP*), Transmembrane Protein 43 (*TMEM43*), and phospholamban (*PLN*). Limitations of genetic testing are also discussed, and a genetic testing recommendation flow chart is provided (Figure 10). Cascade family screening considerations for ACM, including family history, cardiac evaluation, age-related penetrance of disease in at-risk relatives, cascade cardiac investigations, and cascade genetic testing in adults and minors are presented with recommendations and a recommendation flow chart (Figure 11). Treatment considerations for ACM begin with a discussion of risk stratification and ICD decisions with recommendations and a flow chart (Figure 12). Management of ventricular arrhythmia and dysfunction, including angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and antiarrhythmic drugs, is discussed in terms of medical therapies for LV failure, medical therapies for right ventricular (RV) failure, antithrombotic therapy in ACM, and arrhythmia management. Medical therapy recommendation flow charts are shown in Figures 13 and 14. The role of catheter ablation in ACM with recommendations and a recommendation flow chart (Figure 15) is discussed. Finally, the prevention of disease progression is presented in terms of exercise restrictions for ARVC. The clinical exercise questions used to direct the literature search are included, and also exercise definitions, exercise increasing age-related penetrance among genotype-positive relatives, exercise for carriers of pathogenic variants detected incidentally, exercise and relatives of "gene-elusive" patients

with ARVC, exercise increasing arrhythmic risk and structural dysfunction in patients with ARVC, and exercise and other ACMs are discussed. Exercise restriction recommendations are included with a recommendation flow chart (Figure 16), and the metabolic equivalents (METs) associated with common types of endurance exercise (Figure 17).

3.1 Diagnosis and evaluation of arrhythmogenic cardiomyopathy

3.1.1 Evaluation overview

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
Global or regional dysfunction and structural alterations determined by echo, MRI, or RV angiography:		
Echo	Regional RV akinesia, dyskinesia, or aneurysm and 1 of the following (end diastole): a) PLAX RVOT ≥32 mm (PLAX/BSA ≥19 mm/m^2) b) PSAX RVOT ≥36 mm (PSAX/BSA ≥21 mm/m^2) c) Fractional area change ≤33%	Regional RV akinesia, dyskinesia, or aneurysm and 1 of the following (end diastole): a) PLAX RVOT ≥29 mm to <32 mm (PLAX/BSA ≥16 to <19 mm/m^2) b) PSAX RVOT ≥32 to <36 mm (PSAX/BSA ≥18 to <21 mm/m^2) c) Fractional area change >33 to ≤40%
MRI	Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following: a) Ratio RVEDV/BSA ≥110 mL/m^2 (male), ≥100 mL/m^2 (female) b) RVEF ≤40%	Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following: a) Ratio RVEDV/BSA ≥100 to <110 mL/m^2 (male), ≥90 to 100 mL/m^2 (female) b) RVEF >40 to ≤45%
RV angiography	Regional RV akinesia, dyskinesia, or aneurysm	
Tissue characterization of wall		
Endomyocardial biopsy showing fibrous replacement of the RV free wall myocardium in ≥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)
Repolarization abnormalities		
ECG	Inverted T waves in right precordial leads (V_1, V_2, and V_3) or beyond in individuals >14 years of age (in the absence of complete RBBB QRS ≥120ms)	I. Inverted T waves in leads V_1 and V_2 in individuals >14 years of age (in the absence of complete RBBB) or in V_4, V_5, or V_6. II. Inverted T waves in leads V_1, V_2, V_3 and V_4 in individuals >14 years of age in the presence of complete RBBB
Depolarization/conduction abnormalities		
ECG	Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V_1 to V_3)	I. Late potentials by SAECG in ≥1 of 3 parameters in the absence of QRS duration of ≥110ms on the standard ECG: a) Filtered QRS duration (fQRS) ≥114 ms b) Duration of terminal QRS <40 μV (low-amplitude signal duration) ≥38 ms c) Root-mean-square voltage of terminal 40 ms ≤20 μV II. Terminal activation duration of QRS ≥55 ms measured from the nadir of the S wave to the end of the QRS, including R′ in V_1, V_2, or V_3 in the absence of complete RBBB
Arrhythmias		
	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)
Family history		
	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).[14] 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 ventricle; RVEDV = right ventricular end-diastolic volume; RVEF = right ventricular ejection fraction; RVOT = right ventricular outflow tract; SAECG = signal-averaged electrocardiogram; VT = ventricular tachycardia.

3.2 Electrocardiogram features in arrhythmogenic right ventricular cardiomyopathy

3.2.1 Repolarization abnormalities

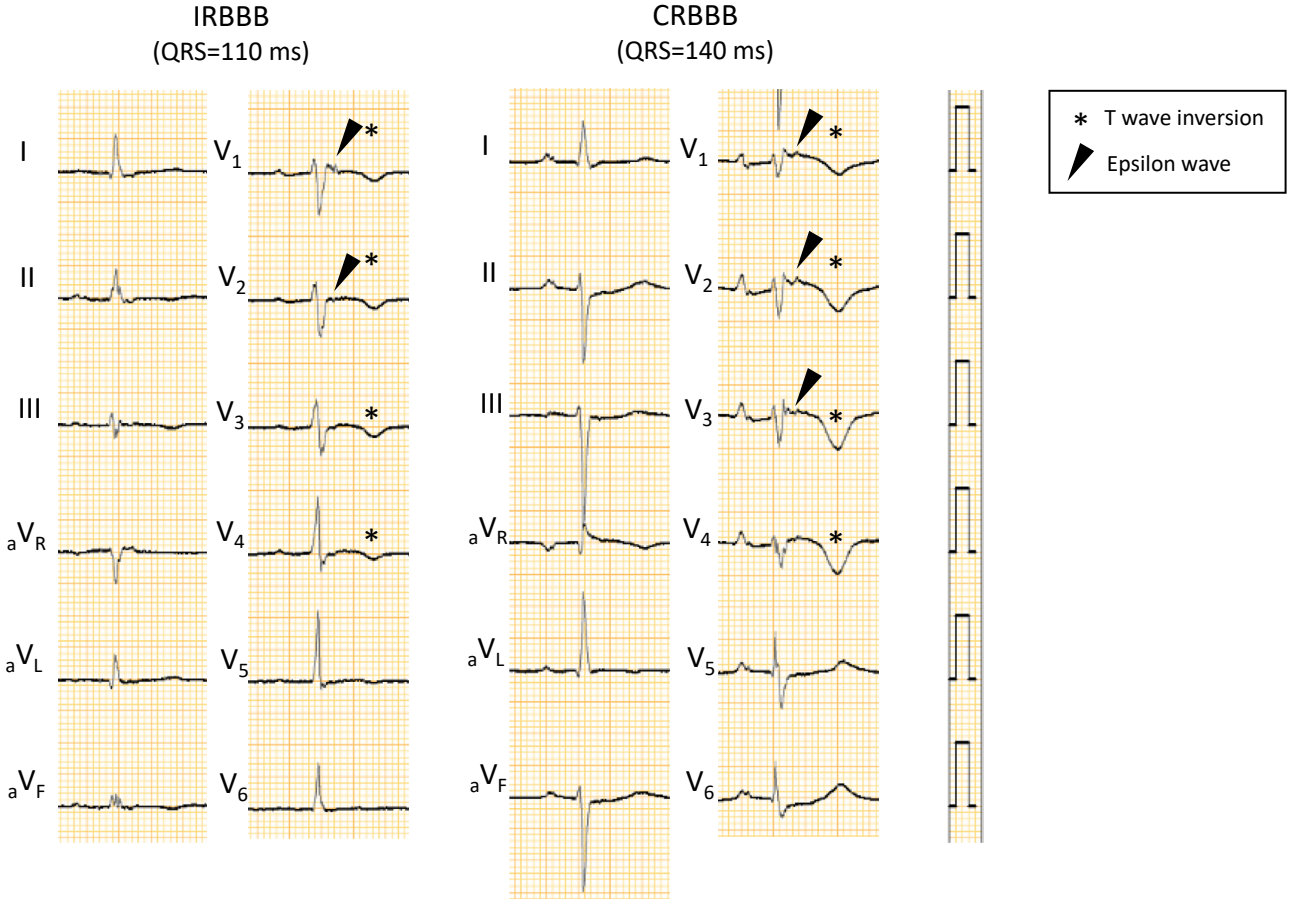

Figure 7 Representative 12-lead electrocardiogram (ECG) obtained from patents with arrhythmogenic right ventricular cardiomyopathy (ARVC) with incomplete right bundle branch block (IRBBB) and complete right bundle branch block (CRBBB). QRS duration of IRBBB and CRBBB was 110 ms and 140 ms, respectively. 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.

3.2.2 Depolarization and conduction abnormalities

3.2.2.1 Prolonged terminal activation duration

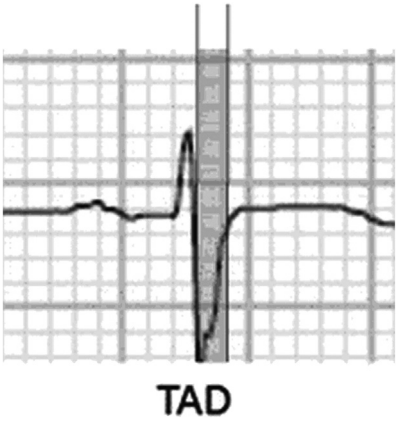

Figure 8 Terminal activation duration (TAD) is measured from the nadir of the S wave to the end of all depolarization deflections and is prolonged if ≥55 ms in any of the V_1–V_3 leads in the absence of complete right bundle branch block. Modified with permission of Oxford University Press on behalf of the European Society of Cardiology.[15]

3.3 Genetic testing

COR	LOE	Recommendations	References
I	C-EO	For individuals and decedents with either a clinical or necropsy diagnosis of ACM, genetic testing of the established ACM-susceptibility genes is recommended.	
I	C-EO	For genetic testing of the established ACM-susceptibility genes, comprehensive analysis of all established genes with full coverage is recommended.	
IIa	C-EO	The interpretation of a cardiac genetic test by a team of providers with expertise in genetics and cardiology can be useful.	

3.3.1 Variant and gene interpretation

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.[16]

3.3.2 Which test to use

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

Gene	Protein type	Predominant type of mutation	OR/EF[17]	Signal: background[27]	Remarks	References
BAG3	Chaperone	Truncating and missense	NA	NA	Also causes myofibrillar myopathy	28
DES	IF	Truncating and missense	NA	NA	Also causes myofibrillar myopathy	29
DSC2	Desm	Truncating and missense	NT 2.15 (EF 0.53) T 21.5* (EF 0.95)	ns ns	Rare	30
DSG2	Desm	Truncating and missense	NT 2.83* (EF 0.65) T 19.8* (EF 0.95)	2:1* (NT/T)	Rarely recessive	31
DSP	Desm	Truncating and missense	NT 2.1* (EF 0.52) T 89.9* (EF 0.99)	ns ns	Recessive: Carvajal syndrome	32,33
FLNC	Actin crosslink	Truncating and missense	NA	NA	Also causes myofibrillar myopathy	34
JUP	Desm	Missense	NT 7.8* (EF 0.87) T 28.1 (EF –)		Recessive: Naxos syndrome	35,36
LDB3	Z-band	Missense	NA	NA	Cypher/ZASP	37
LMNA	NE	Truncating and missense	NA	NA	AV block; CD	38
NKX2-5	Homeobox	Truncating and missense	NA	NA	AV block, CD, CHD	39
PKP2	Desm	Truncating	NT 1.3 (EF 0.23) T 484.7* (EF 1.0)	10:1* 42:1*	Large deletions 1-2%	40
PLN	Ca	Missense, nonsense, and deletion	NA	NA	Predominantly R14del	41,42
RBM20	Splice factor	Missense	NA	NA	Mostly in exon 9	43
SCN5A	Sodium channel	Mostly missense	NA	NA	Brugada, SND, CD	44
TMEM43	NE	Missense	NT 0.76 (EF –) T 13 (EF –)	ns	p.S358L disease-causing; also called LUMA	45

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.[17] Other genes that have been identified in ACM with insufficient or conflicting evidence are: *ABCC9*,[18] *TGFB3*,[19] *TTN*,[20] *CTNNA3*,[21] sarcomeric genes (*MYH7, MYBPC3*),[22,23] *SCN3B*,[23] *CDH2*,[24,25] *TJP1*.[26]

3.3.3 Advantages and disadvantages of various methods

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.

3.3.4 The use of genetic testing in risk stratification and management

3.3.4.1 Specific variants and genes

3.3.4.1.1 Desmosomal genes

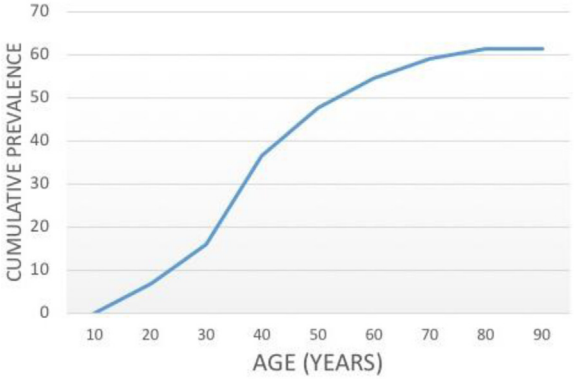

Figure 9 Cumulative prevalence of disease expression in family members at risk of arrhythmogenic right ventricular cardiomyopathy (ARVC).[46]

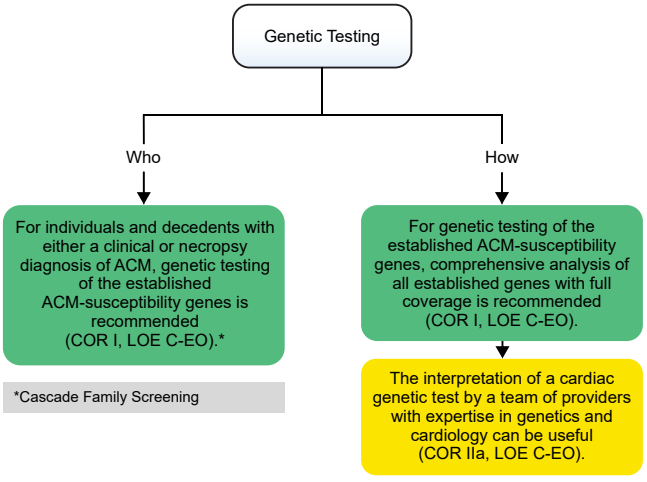

Figure 10 Genetic testing recommendations. * = Cascade family screening: see Section 3.4. ACM = arrhythmogenic cardiomyopathy; COR = Class of Recommendation; LOE = Level of Evidence. Colors correspond to COR in Figure 1.

3.4 Cascade family screening

3.4.1 Family history

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

3.4.2 Age-related penetrance of disease in at-risk relatives

COR	LOE	Recommendations	References
I	B-NR	**It is recommended that first-degree relatives undergo clinical evaluation every 1–3 years starting at 10–12 years of age.**	34,47–52
I	B-NR	**Cardiovascular evaluation should include 12-lead ECG, ambulatory ECG, and cardiac imaging.**	46,51–57

3.4.3 Cascade cardiac investigations

COR	LOE	Recommendations	References
IIb	C-LD	**Exercise stress testing (arrhythmia provocation) may be considered as a useful adjunct to cardiovascular evaluation.**	58

3.4.4 Cascade genetic testing

COR	LOE	Recommendations	References
IIb	C-EO	**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.**	

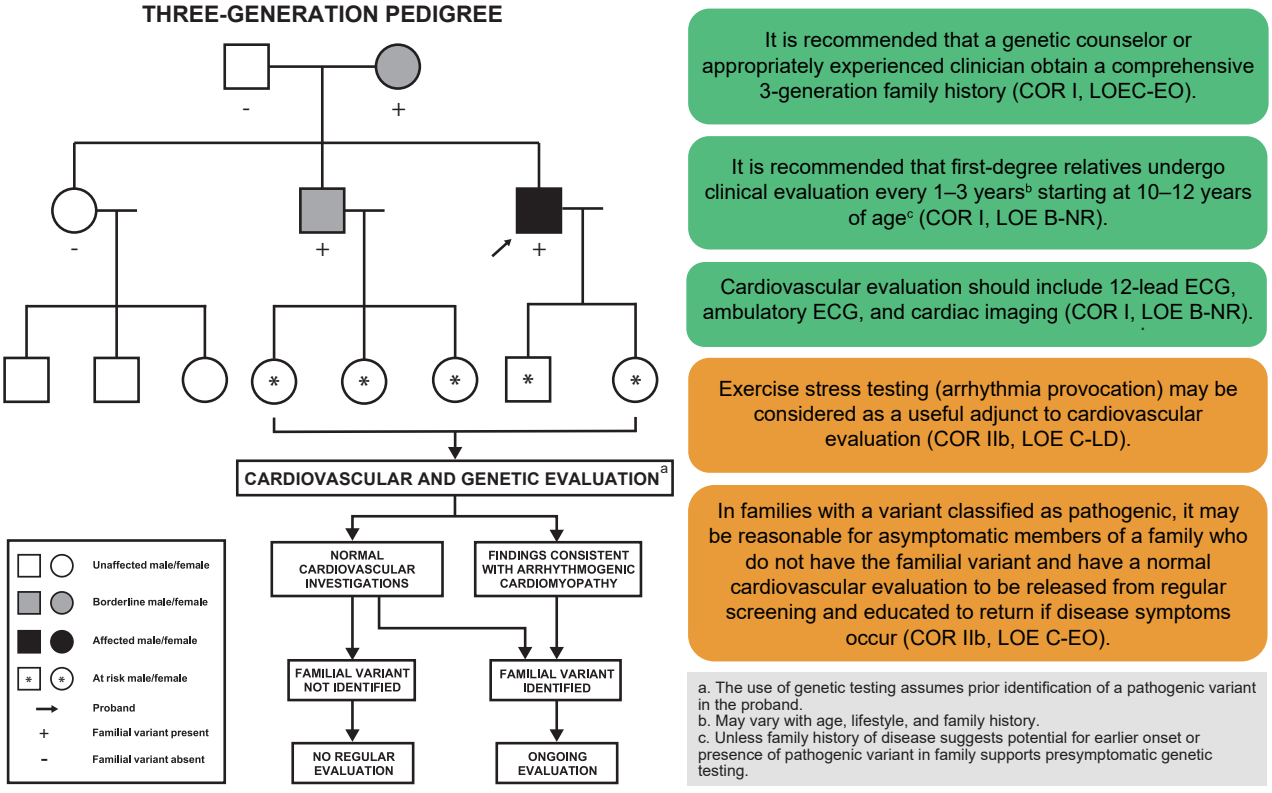

Figure 11 Summary of family screening recommendations. COR = Class of Recommendation; ECG = electrocardiogram; LOE = Level of Evidence. Colors correspond to COR in Figure 1.

3.5 Risk stratification and implantable cardioverter defibrillator decisions

COR	LOE	Recommendations	References
I	C-EO	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.	
I	B-NR	In individuals with ACM who have suffered a cardiac arrest with VT or VF, an ICD is recommended.	59–64
I	B-NR	In individuals with ACM who have sustained VT not hemodynamically tolerated, an ICD is recommended.	59–62,64
I	B-NR	In individuals with ACM (other than ARVC) and hemodynamically tolerated VT, an ICD is recommended.	50,65
I	B-R	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.	64,66–70
IIa	B-R	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.	69
IIa	B-NR	In individuals with ACM and syncope suspected to be due to a ventricular arrhythmia, an ICD is reasonable.	59–62,66,68–74
IIa	B-NR	In individuals with ARVC with hemodynamically tolerated sustained VT, an ICD is reasonable.	60–62,72
IIa	B-NR	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.*	61,62,72,75
IIa	B-NR	In individuals with phospholamban cardiomyopathy and LVEF $<$45% or NSVT, an ICD is reasonable.	50
IIa	B-NR	In individuals with lamin A/C ACM and two or more of the following: LVEF $<$45%, NSVT, male sex, an ICD is reasonable.	65
IIa	C-LD	In individuals with lamin A/C ACM and an indication for pacing, an ICD with pacing capabilities is reasonable.	49,74,76
IIa	C-LD	In individuals with *FLNC* ACM and an LVEF $<$45%, an ICD is reasonable.	34
IIb	B-NR	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.*	61,62,72,75

*Major criteria: nonsustained ventricular tachycardia (NSVT), inducibility to VT at electrophysiology study (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.

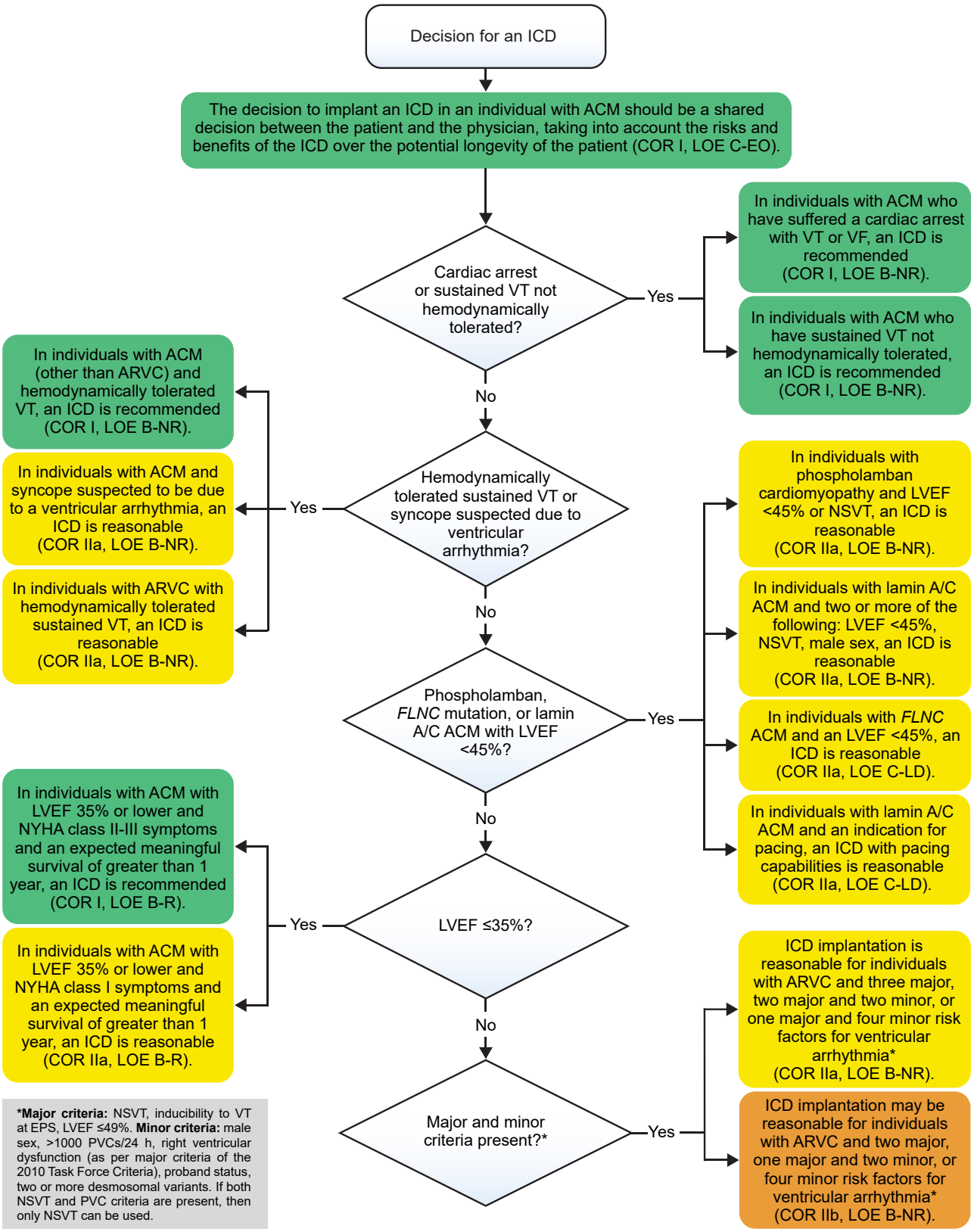

Figure 12 Implantable cardioverter defibrillator (ICD) recommendations. See Section 5 for recommendations regarding left ventricular noncompaction. ACM = arrhythmogenic cardiomyopathy; ARVC = arrhythmogenic right ventricular cardiomyopathy; COR = Class of Recommendation; EPS = electrophysiology studies; *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.

3.6 Management of ventricular arrhythmia and dysfunction

3.6.1 Medications Including Angiotensin-Converting Enzyme Inhibitors, Beta-Blockers, and Antiarrhythmic Drugs

3.6.1.1 Medical Therapies for Right Ventricular Failure

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

3.6.1.2 Antithrombotic therapy in arrhythmogenic cardiomyopathy

COR	LOE	Recommendations	References
I	B-NR	In individuals with ACM, in the presence of atrial fibrillation, intracavitary thrombosis, or venous/systemic thromboembolism, anticoagulant therapy is recommended.	77
IIb	C-EO	Antithrombotic therapy may be reasonable in individuals with LV or RV aneurysm.	

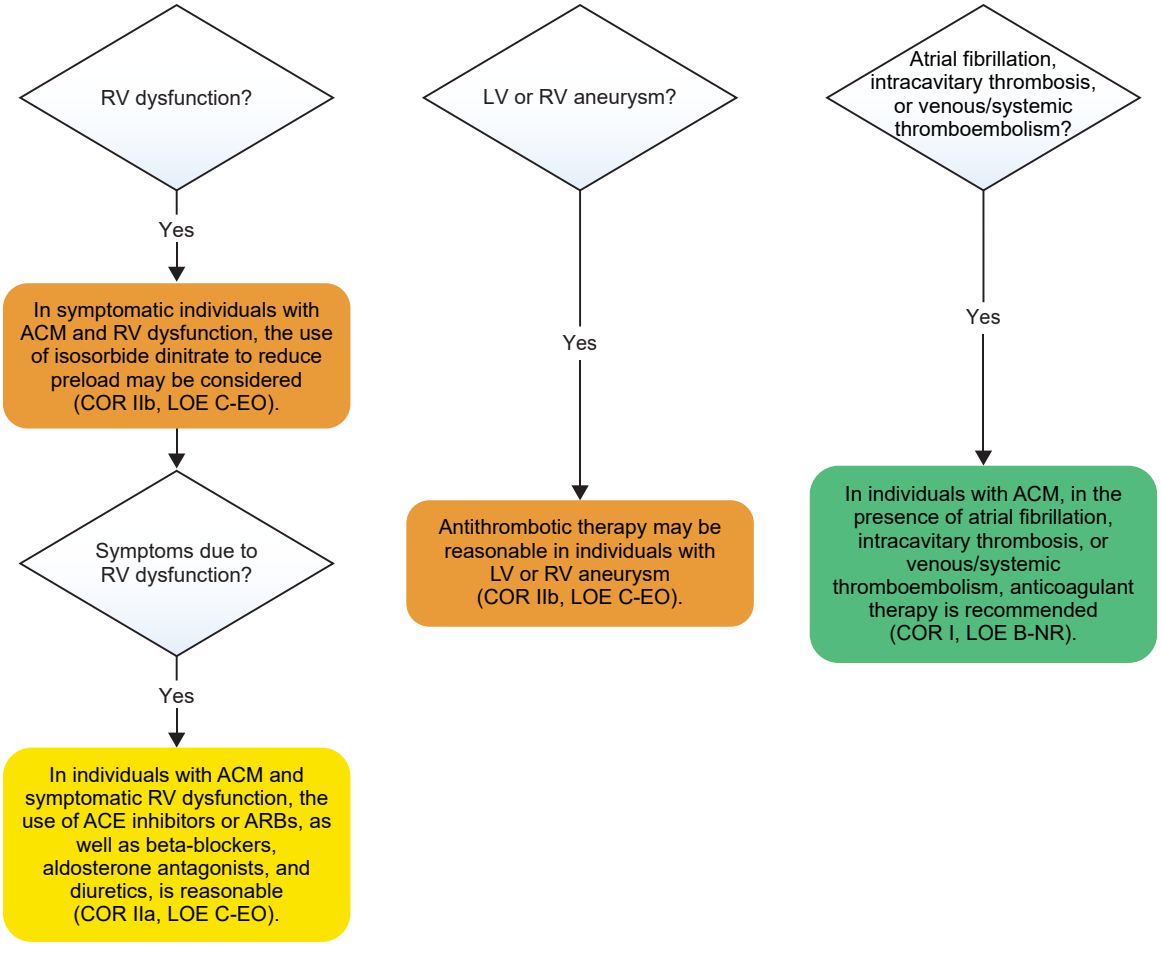

Figure 13 Recommendations for ventricular dysfunction and antithrombotic medical therapy in individuals with arrhythmogenic cardiomyopathy (ACM). ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; COR = Class of Recommendation; LOE = Level of Evidence; LV = left ventricle; RV =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

3.6.1.3 Arrhythmia management

COR	LOE	Recommendations	References
I	C-LD	**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.**	78
IIa	C-EO	**Beta-blocker therapy is reasonable in individuals with ACM who do not have an ICD.**	
IIb	B-NR C-LD	**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.**	72,79,80
IIb	C-LD	**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.**	81

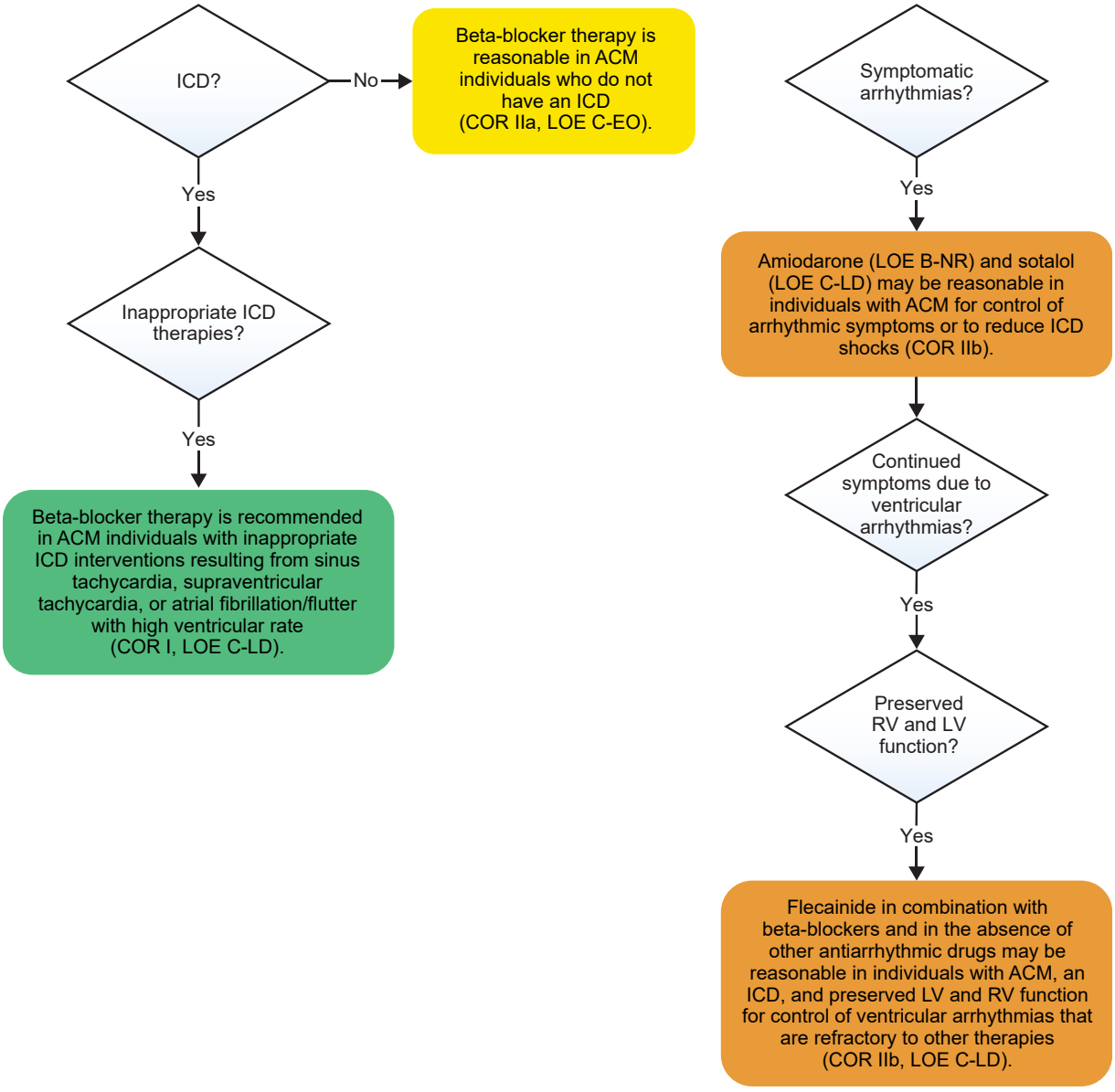

Figure 14 Medical therapy recommendations for arrhythmias. ACM = arrhythmogenic cardiomyopathy; COR = Class of Recommendation; ICD = implantable cardioverter defibrillator; LOE = Level of Evidence; LV = left ventricle; RV = right ventricle. Colors correspond to COR in Figure 1.

3.6.2 Role of catheter ablation

COR	LOE	Recommendations	References
IIa	B-NR	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.	82–92
IIa	B-NR	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.	86,88–92
IIa	C-EO	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.	
IIb	C-LD	Individuals with ACM and recurrent symptomatic sustained VT in whom medical therapy has not failed may be considered for catheter ablation.	86,88,90

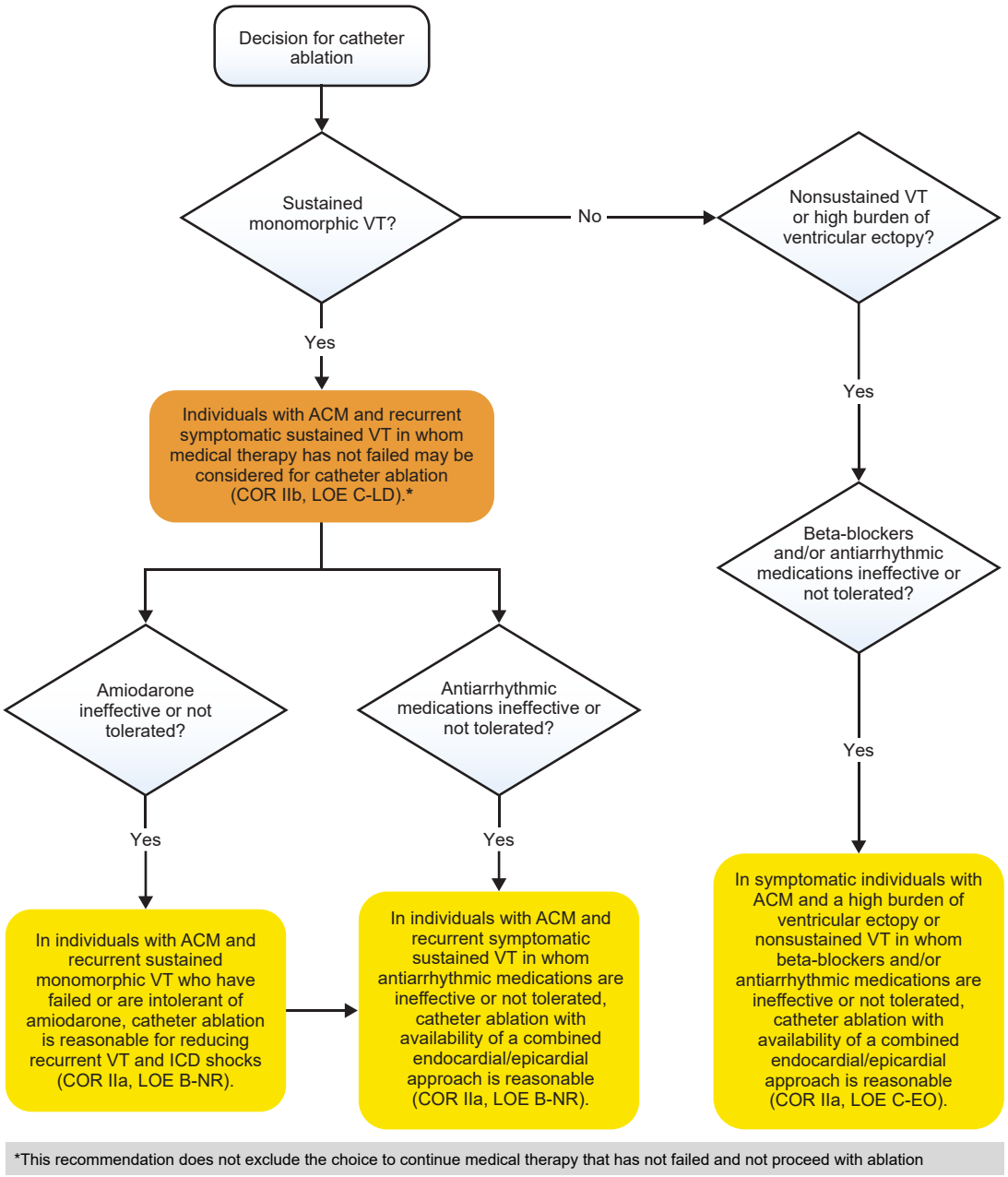

Figure 15 Catheter ablation recommendations for individuals with arrhythmogenic cardiomyopathy (ACM). COR = Class of Recommendation; ICD = implantable cardioverter defibrillator; LOE = Level of Evidence; VT = ventricular tachycardia. Colors correspond to COR in Figure 1.

3.7 Prevention of disease progression

3.7.1 Exercise and other arrhythmogenic cardiomyopathies

COR	LOE	Recommendations	References
I	B-NR	**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.**	93–96
III: Harm	B-NR	**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.**	72,93–98

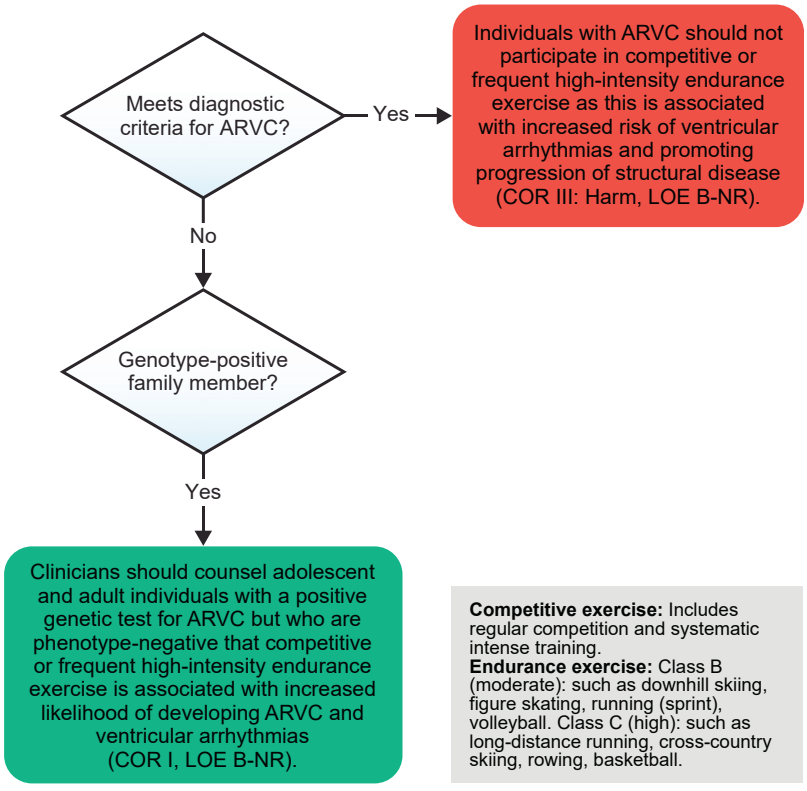

Figure 16 Exercise recommendations for individuals with arrhythmogenic right ventricular cardiomyopathy (ARVC). COR = Class of Recommendation; LOE = Level of Evidence. Colors correspond to COR in Figure 1.

METs	Examples of METs associated with endurance exercise
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)
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/).[99,100] 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,[93,96,97,101] 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[99] and to aid in discussions with patients and families.

Section 4 Disease mechanisms

This section presents an overview of the basic science details of the mechanisms responsible for the forms of ACM (Figure 18). Desmosomal defects, ion channel defects, sarcomeric defects, metabolic defects, mitochondrial forms, and histiocytoid (oncocytic) cardiomyopathy are discussed.

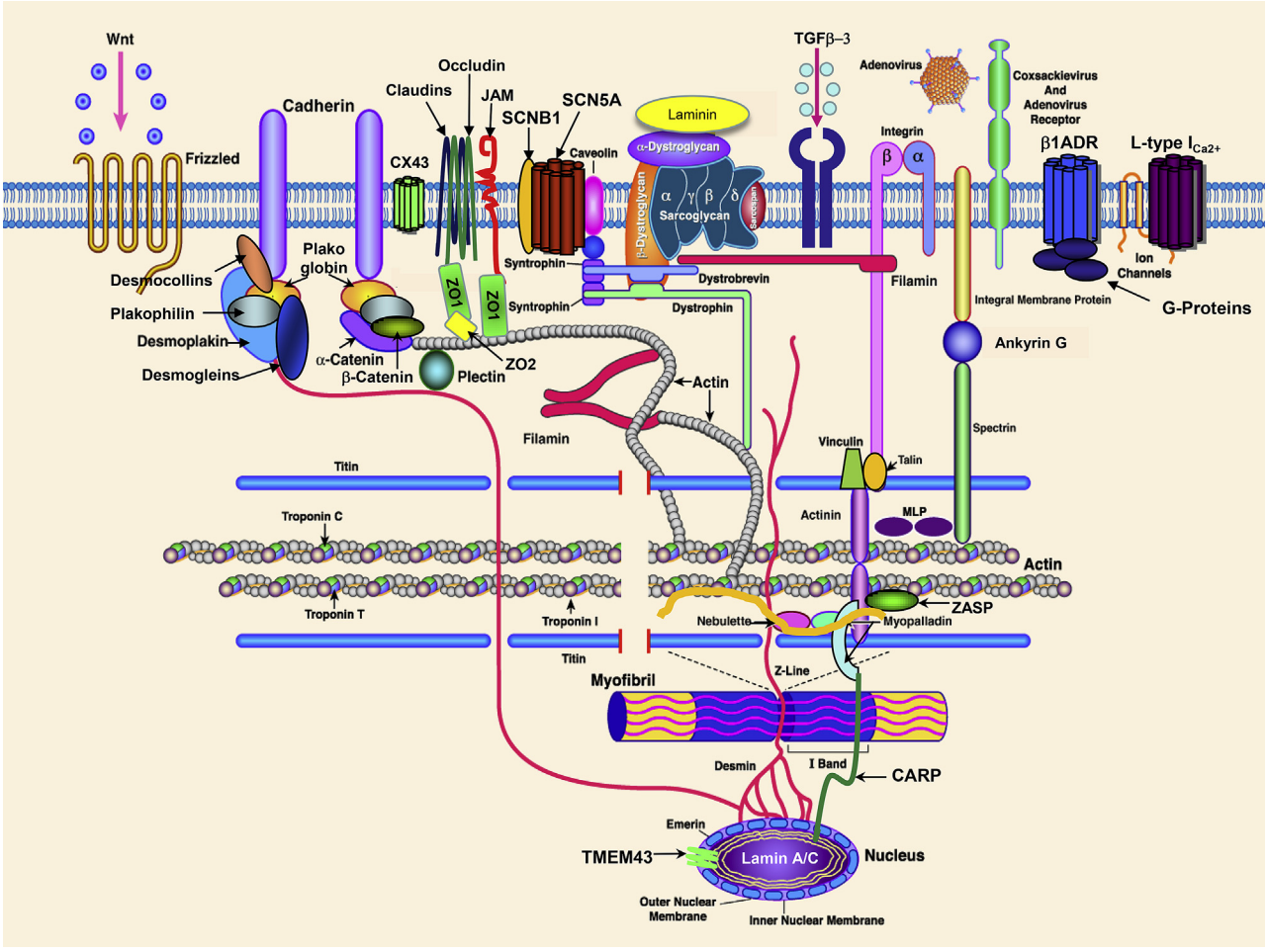

Figure 18 Disease mechanisms for arrhythmogenic cardiomyopathy. Cardiomyocyte showing the extracellular matrix, sarcolemma, sarcomere, nucleus, and key proteins that provide structure for ventricular function and cardiac rhythm. Descriptions of the functions of these proteins are included in section 4.

Section 5 Other disorders

This section discusses other disorders of ACM, including amyloidosis, Brugada syndrome, potassium channels (KCNQ1, KCNH2, and TRMP4), phospholamban, and LVNC. Recommendations for amyloidosis arrhythmia treatment are presented with a flow chart (Figure 19). LVNC diagnostic methods, diagnostic criteria (Table 5), and treatment are discussed in detail including recommendations and flow charts for diagnosis (Figure 20) and treatment (Figure 21).

COR	LOE	Recommendations	References
I	B-NR	In both symptomatic and asymptomatic individuals with cardiac amyloidosis and second-degree atrioventricular (AV) block type II, high-grade AV block or third-degree AV block, a permanent pacemaker is recommended.	102–105
I	C-EO	In individuals with cardiac amyloidosis who have survived a cardiac arrest, an ICD is recommended if meaningful survival greater than 1 year is expected.	
IIb	B-NR	In individuals with cardiac amyloidosis, the use of digoxin may be considered if used with caution due to the high risk of toxicity.	106
IIb	B-NR	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.	107
IIb	C-LD	In individuals with cardiac amyloidosis and symptomatic atrial arrhythmias, cardiac ablation may be considered.	108
IIb	C-EO	In individuals with cardiac amyloidosis and symptomatic atrial arrhythmias, the use of sotalol, dofetilide, or amiodarone may be considered.	

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.

5.1 Amyloidosis

COR	LOE	Recommendations	References
I	B-NR	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.	109–111
I	B-NR	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.	112
I	B-NR	Anticoagulation is recommended in individuals with LVNC with atrial fibrillation and in those with previous embolic events.	113
IIa	B-NR	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.	109,111
IIa	B-NR	ICD implantation is reasonable in individuals with LVNC and evidence of nonsustained VT associated with a reduced ejection fraction.	112,114
IIb	B-NR	Anticoagulation may be reasonable in individuals with LVNC with evidence of ventricular dysfunction.	113
IIb	B-NR	In individuals with suspected LVNC, the diagnostic criteria by echocardiography or cardiac magnetic resonance imaging (CMR), measured as the maximal ratio of noncompaction to compaction (NC/C), may be reasonable for establishing a diagnosis.	115–119
IIb	B-NR	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.	118–120

Table 5 Diagnostic criteria for left ventricular noncompaction (LVNC)

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

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

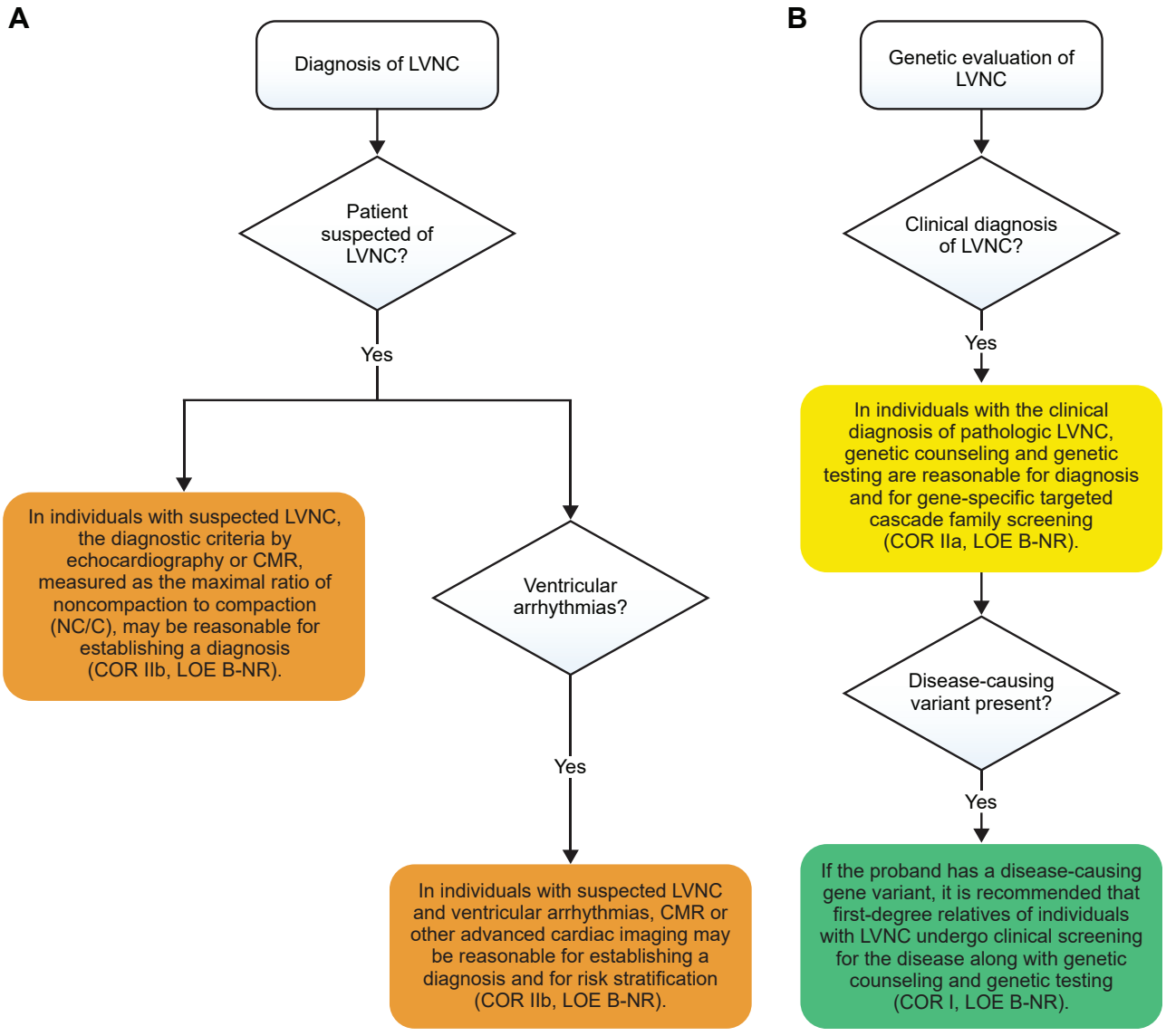

Figure 20 Diagnosis and risk stratification of left ventricular noncompaction (LVNC) (**A**) and family and genetic evaluation of LVNC (**B**). CMR = cardiac magnetic resonance imaging; COR = Class of Recommendation; LOE = Level of Evidence; NC/C = maximum noncompaction to compaction ratio. Colors correspond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

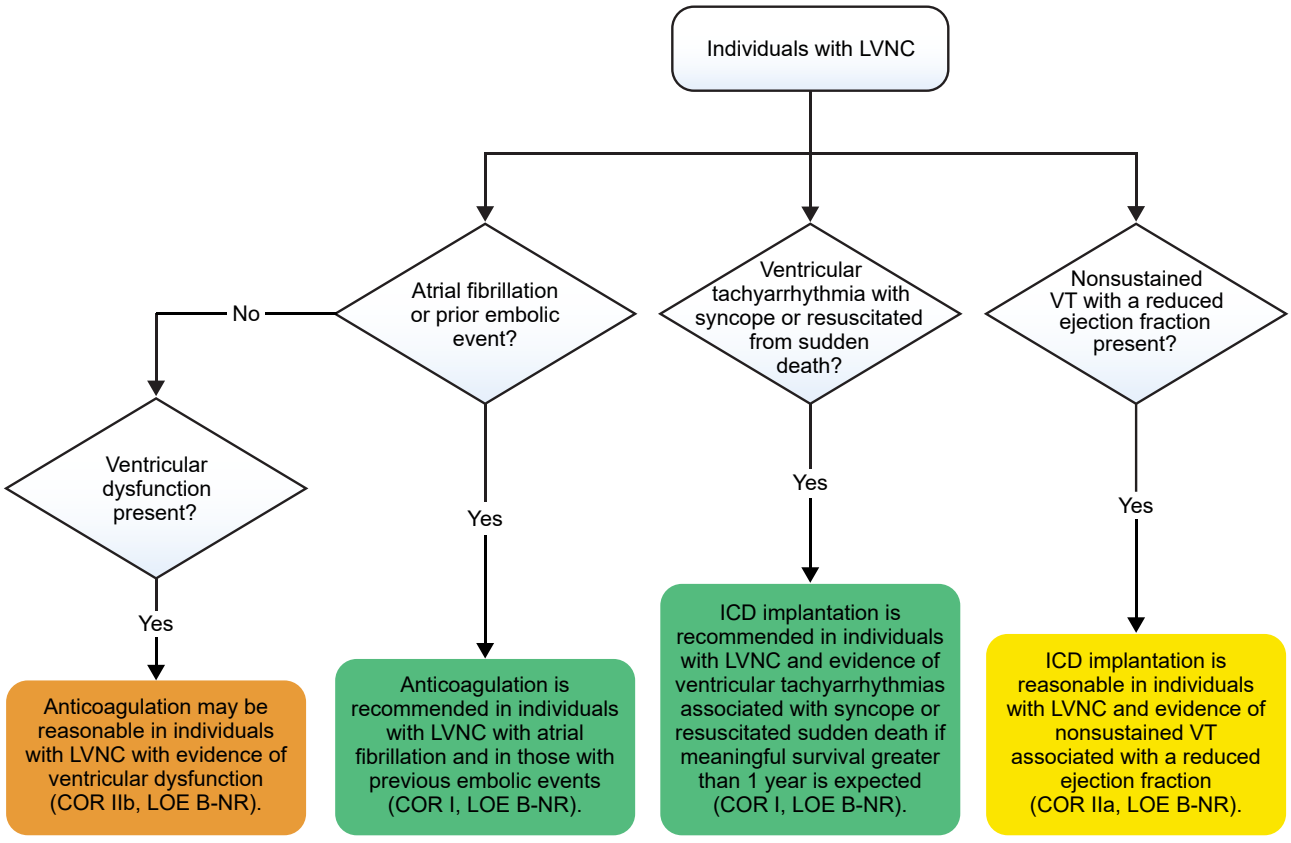

Figure 21 Left ventricular noncompaction (LVNC) treatment recommendations. Anticoagulation refers to vitamin K antagonists and direct oral anticoagulants. Children are often administered aspirin. COR = Class of Recommendation; ICD = implantable cardioverter defibrillator; LOE = Level of Evidence; LVNC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

5.2 Left ventricular noncompaction

Section 6 Future directions and research recommendations

This section lists future directions for the understanding of mechanisms responsible for the development and progression of ACM and lists recommended topics for research.

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.2019.09.019.

References

1. Indik JH, Patton KK, Beardsall M, et al. HRS Clinical Document Development Methodology Manual and Policies: Executive summary. Heart Rhythm 2017; 14:e495–e500.
2. Halperin JL, Levine GN, Al-Khatib SM, et al. Further Evolution of the ACC/AHA Clinical Practice Guideline Recommendation Classification System: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2016;133:1426–1428.
3. Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Heart Rhythm 2018;15:e73–e189.
4. Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities. Heart Rhythm 2008; 5:e1–e62.
5. Ackerman MJ, Priori SG, Willems S, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies. Heart Rhythm 2011;8:1308–1339.
6. Priori SG, Wilde AA, Horie M, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. Heart Rhythm 2013;10:1932–1963.
7. Yancy CW, Jessup M, Bozkurt B, et al. 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: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol 2016;68:1476–1488.
8. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;62:e147–e239.
9. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37:2129–2200.
10. Marcus FI, McKenna WJ, Sherrill D, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. Circulation 2010;121:1533–1541.
11. Hershberger RE, Givertz MM, Ho CY, Judge DP, Kantor PF, McBride KL, Morales A, Taylor MRG, Vatta M, Ware SM. Genetic Evaluation of Cardiomyopathy-A Heart Failure Society of America Practice Guideline. J Card Fail 2018;24:281–302.
12. Corrado D, Wichter T, Link MS, et al. Treatment of Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia: An International Task Force Consensus Statement. Circulation 2015;132:441–453.

13. Hoshijima M. Mechanical stress-strain sensors embedded in cardiac cytoskeleton: Z disk, titin, and associated structures. Am J Physiol Heart Circ Physiol 2006; 290:H1313–H1325.
14. Cox MG, van der Smagt JJ, Noorman M, et al. Arrhythmogenic right ventricular dysplasia/cardiomyopathy diagnostic task force criteria: impact of new task force criteria. Circ Arrhythm Electrophysiol 2010;3:126–133.
15. Nunes de Alencar Neto J, Baranchuk A, Bayes-Genis A, Bayes de Luna A. Arrhythmogenic right ventricular dysplasia/cardiomyopathy: an electrocardiogram-based review. Europace 2018;20:f3–f12.
16. Plon SE, Eccles DM, Easton D, Foulkes WD, Genuardi M, Greenblatt MS, Hogervorst FB, Hoogerbrugge N, Spurdle AB, Tavtigian SV. Sequence variant classification and reporting: recommendations for improving the interpretation of cancer susceptibility genetic test results. Hum Mutat 2008;29:1282–1291.
17. Walsh R, Thomson KL, Ware JS, et al. Reassessment of Mendelian gene pathogenicity using 7,855 cardiomyopathy cases and 60,706 reference samples. Genet Med 2017;19:192–203.
18. Bienengraeber M, Olson TM, Selivanov VA, et al. ABCC9 mutations identified in human dilated cardiomyopathy disrupt catalytic KATP channel gating. Nat Genet 2004;36:382–387.
19. Rampazzo A, Nava A, Malacrida S, Beffagna G, Bauce B, Rossi V, Zimbello R, Simionati B, Basso C, Thiene G, Towbin JA, Danieli GA. Mutation in human desmoplakin domain binding to plakoglobin causes a dominant form of arrhythmogenic right ventricular cardiomyopathy. Am J Hum Genet 2002;71:1200–1206.
20. Taylor M, Graw S, Sinagra G, et al. Genetic variation in titin in arrhythmogenic right ventricular cardiomyopathy-overlap syndromes. Circulation 2011; 124:876–885.
21. van Hengel J, Calore M, Bauce B, et al. Mutations in the area composita protein alphaT-catenin are associated with arrhythmogenic right ventricular cardiomyopathy. Eur Heart J 2013;34:201–210.
22. Murray B, Hoorntje ET, Te Riele A, et al. Identification of sarcomeric variants in probands with a clinical diagnosis of arrhythmogenic right ventricular cardiomyopathy (ARVC). J Cardiovasc Electrophysiol 2018;29:1004–1009.
23. Medeiros-Domingo A, Saguner AM, Magyar I, Bahr A, Akdis D, Brunckhorst C, Duru F, Berger W. Arrhythmogenic right ventricular cardiomyopathy: implications of next-generation sequencing in appropriate diagnosis. Europace 2017; 19:1063–1069.
24. Mayosi BM, Fish M, Shaboodien G, et al. Identification of Cadherin 2 (CDH2) Mutations in Arrhythmogenic Right Ventricular Cardiomyopathy. Circ Cardiovasc Genet 2017;10.
25. Turkowski KL, Tester DJ, Bos JM, Haugaa KH, Ackerman MJ. Whole exome sequencing with genomic triangulation implicates CDH2-encoded N-cadherin as a novel pathogenic substrate for arrhythmogenic cardiomyopathy. Congenit Heart Dis 2017;12:226–235.
26. De Bortoli M, Postma AV, Poloni G, et al. Whole-Exome Sequencing Identifies Pathogenic Variants in TJP1 Gene Associated With Arrhythmogenic Cardiomyopathy. Circ Genom Precis Med 2018;11:e002123.
27. Kapplinger JD, Landstrom AP, Salisbury BA, et al. Distinguishing arrhythmogenic right ventricular cardiomyopathy/dysplasia-associated mutations from background genetic noise. J Am Coll Cardiol 2011;57:2317–2327.
28. Norton N, Li D, Rieder MJ, et al. Genome-wide studies of copy number variation and exome sequencing identify rare variants in BAG3 as a cause of dilated cardiomyopathy. Am J Hum Genet 2011;88:273–282.
29. Hedberg C, Melberg A, Kuhl A, Jenne D, Oldfors A. Autosomal dominant myofibrillar myopathy with arrhythmogenic right ventricular cardiomyopathy 7 is caused by a DES mutation. Eur J Hum Genet 2012;20:984–985.
30. Syrris P, Ward D, Evans A, Asimaki A, Gandjbakhch E, Sen-Chowdhry S, McKenna WJ. Arrhythmogenic right ventricular dysplasia/cardiomyopathy associated with mutations in the desmosomal gene desmocollin-2. Am J Hum Genet 2006;79:978–984.
31. Awad MM, Dalal D, Cho E, Amat-Alarcon N, James C, Tichnell C, Tucker A, Russell SD, Bluemke DA, Dietz HC, Calkins H, Judge DP. DSG2 mutations contribute to arrhythmogenic right ventricular dysplasia/cardiomyopathy. Am J Hum Genet 2006;79:136–142.
32. Yang Z, Bowles NE, Scherer SE, et al. Desmosomal dysfunction due to mutations in desmoplakin causes arrhythmogenic right ventricular dysplasia/cardiomyopathy. Circ Res 2006;99:646–655.
33. Norgett EE, Hatsell SJ, Carvajal-Huerta L, Cabezas JC, Common J, Purkis PE, Whittock N, Leigh IM, Stevens HP, Kelsell DP. Recessive mutation in desmoplakin disrupts desmoplakin-intermediate filament interactions and causes dilated cardiomyopathy, woolly hair and keratoderma. Hum Mol Genet 2000; 9:2761–2766.
34. Ortiz-Genga MF, Cuenca S, Dal Ferro M, et al. Truncating FLNC mutations are associated with high-risk dilated and arrhythmogenic cardiomyopathies. J Am Coll Cardiol 2016;68:2440–2451.
35. Asimaki A, Syrris P, Wichter T, Matthias P, Saffitz JE, McKenna WJ. A novel dominant mutation in plakoglobin causes arrhythmogenic right ventricular cardiomyopathy. Am J Hum Genet 2007;81:964–973.
36. McKoy G, Protonotarios N, Crosby A, Tsatsopoulou A, Anastasakis A, Coonar A, Norman M, Baboonian C, Jeffery S, McKenna WJ. Identification of a deletion in plakoglobin in arrhythmogenic right ventricular cardiomyopathy with palmoplantar keratoderma and woolly hair (Naxos disease). Lancet 2000; 355:2119–2124.
37. Vatta M, Mohapatra B, Jimenez S, et al. Mutations in Cypher/ZASP in patients with dilated cardiomyopathy and left ventricular non-compaction. J Am Coll Cardiol 2003;42:2014–2027.
38. Quarta G, Syrris P, Ashworth M, Jenkins S, Zuborne Alapi K, Morgan J, Muir A, Pantazis A, McKenna WJ, Elliott PM. Mutations in the Lamin A/C gene mimic arrhythmogenic right ventricular cardiomyopathy. Eur Heart J 2012; 33:1128–1136.
39. Pashmforoush M, Lu JT, Chen H, et al. Nkx2-5 pathways and congenital heart disease; loss of ventricular myocyte lineage specification leads to progressive cardiomyopathy and complete heart block. Cell 2004;117:373–386.
40. Gerull B, Heuser A, Wichter T, et al. Mutations in the desmosomal protein plakophilin-2 are common in arrhythmogenic right ventricular cardiomyopathy. Nat Genet 2004;36:1162–1164.
41. Schmitt JP, Kamisago M, Asahi M, Li GH, Ahmad F, Mende U, Kranias EG, MacLennan DH, Seidman JG, Seidman CE. Dilated cardiomyopathy and heart failure caused by a mutation in phospholamban. Science 2003;299:1410–1413.
42. van der Zwaag PA, van Rijsingen IA, Asimaki A, et al. Phospholamban R14del mutation in patients diagnosed with dilated cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy: evidence supporting the concept of arrhythmogenic cardiomyopathy. Eur J Heart Fail 2012;14:1199–1207.
43. Brauch KM, Karst ML, Herron KJ, de Andrade M, Pellikka PA, Rodeheffer RJ, Michels VV, Olson TM. Mutations in ribonucleic acid binding protein gene cause familial dilated cardiomyopathy. J Am Coll Cardiol 2009;54:930–941.
44. McNair WP, Ku L, Taylor MR, Fain PR, Dao D, Wolfel E, Mestroni L, Familial Cardiomyopathy Registry Research G. SCN5A mutation associated with dilated cardiomyopathy, conduction disorder, and arrhythmia. Circulation 2004; 110:2163–2167.
45. Merner ND, Hodgkinson KA, Haywood AF, et al. Arrhythmogenic right ventricular cardiomyopathy type 5 is a fully penetrant, lethal arrhythmic disorder caused by a missense mutation in the TMEM43 gene. Am J Hum Genet 2008; 82:809–821.
46. Quarta G, Muir A, Pantazis A, Syrris P, Gehmlich K, Garcia-Pavia P, Ward D, Sen-Chowdhry S, Elliott PM, McKenna WJ. Familial evaluation in arrhythmogenic right ventricular cardiomyopathy: impact of genetics and revised task force criteria. Circulation 2011;123:2701–2709.
47. Hodgkinson KA, Connors SP, Merner N, Haywood A, Young TL, McKenna WJ, Gallagher B, Curtis F, Bassett AS, Parfrey PS. The natural history of a genetic subtype of arrhythmogenic right ventricular cardiomyopathy caused by a p.S358L mutation in TMEM43. Clin Genet 2013;83:321–331.
48. van Tintelen JP, Van Gelder IC, Asimaki A, et al. Severe cardiac phenotype with right ventricular predominance in a large cohort of patients with a single missense mutation in the DES gene. Heart Rhythm 2009;6:1574–1583.
49. Hasselberg NE, Haland TF, Saberniak J, Brekke PH, Berge KE, Leren TP, Edvardsen T, Haugaa KH. Lamin A/C cardiomyopathy: young onset, high penetrance, and frequent need for heart transplantation. Eur Heart J 2018;39:853–860.
50. van Rijsingen IA, van der Zwaag PA, Groeneweg JA, et al. Outcome in phospholamban R14del carriers: results of a large multicentre cohort study. Circ Cardiovasc Genet 2014;7:455–465.
51. Te Riele AS, James CA, Groeneweg JA, et al. Approach to family screening in arrhythmogenic right ventricular dysplasia/cardiomyopathy. Eur Heart J 2016; 37:755–763.
52. Bauce B, Rampazzo A, Basso C, et al. Clinical phenotype and diagnosis of arrhythmogenic right ventricular cardiomyopathy in pediatric patients carrying desmosomal gene mutations. Heart Rhythm 2011;8:1686–1695.
53. Groeneweg JA, Bhonsale A, James CA, et al. Clinical Presentation, Long-Term Follow-Up, and Outcomes of 1001 Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy Patients and Family Members. Circ Cardiovasc Genet 2015;8:437–446.
54. Dalal D, James C, Devanagondi R, Tichnell C, Tucker A, Prakasa K, Spevak PJ, Bluemke DA, Abraham T, Russell SD, Calkins H, Judge DP. Penetrance of mutations in plakophilin-2 among families with arrhythmogenic right ventricular dysplasia/cardiomyopathy. J Am Coll Cardiol 2006;48:1416–1424.
55. Hamid MS, Norman M, Quraishi A, Firoozi S, Thaman R, Gimeno JR, Sachdev B, Rowland E, Elliott PM, McKenna WJ. Prospective evaluation of relatives for familial arrhythmogenic right ventricular cardiomyopathy/dysplasia reveals a need to broaden diagnostic criteria. J Am Coll Cardiol 2002; 40:1445–1450.

56. te Riele AS, James CA, Rastegar N, Bhonsale A, Murray B, Tichnell C, Judge DP, Bluemke DA, Zimmerman SL, Kamel IR, Calkins H, Tandri H. Yield of serial evaluation in at-risk family members of patients with ARVD/C. J Am Coll Cardiol 2014;64:293–301.
57. Protonotarios A, Anastasakis A, Panagiotakos DB, Antoniades L, Syrris P, Vouliotis A, Stefanadis C, Tsatsopoulou A, McKenna WJ, Protonotarios N. Arrhythmic risk assessment in genotyped families with arrhythmogenic right ventricular cardiomyopathy. Europace 2016;18:610–616.
58. Perrin MJ, Angaran P, Laksman Z, Zhang H, Porepa LF, Rutberg J, James C, Krahn AD, Judge DP, Calkins H, Gollob MH. Exercise testing in asymptomatic gene carriers exposes a latent electrical substrate of arrhythmogenic right ventricular cardiomyopathy. J Am Coll Cardiol 2013;62:1772–1779.
59. Corrado D, Leoni L, Link MS, et al. Implantable cardioverter-defibrillator therapy for prevention of sudden death in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia. Circulation 2003;108:3084–3091.
60. Hulot JS, Jouven X, Empana JP, Frank R, Fontaine G. Natural history and risk stratification of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Circulation 2004;110:1879–1884.
61. Link MS, Laidlaw D, Polonsky B, Zareba W, McNitt S, Gear K, Marcus F, Estes NA 3rd. Ventricular arrhythmias in the North American multidisciplinary study of ARVC: predictors, characteristics, and treatment. J Am Coll Cardiol 2014;64:119–125.
62. Orgeron GM, James CA, Te Riele A, Tichnell C, Murray B, Bhonsale A, Kamel IR, Zimmerman SL, Judge DP, Crosson J, Tandri H, Calkins H. Implantable Cardioverter-Defibrillator Therapy in Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy: Predictors of Appropriate Therapy, Outcomes, and Complications. J Am Heart Assoc 2017;6.
63. Hodgkinson KA, Parfrey PS, Bassett AS, Kupprion C, Drenckhahn J, Norman MW, Thierfelder L, Stuckless SN, Dicks EL, McKenna WJ, Connors SP. The impact of implantable cardioverter-defibrillator therapy on survival in autosomal-dominant arrhythmogenic right ventricular cardiomyopathy (ARVD5). J Am Coll Cardiol 2005;45:400–408.
64. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352:225–237.
65. van Rijsingen IA, Arbustini E, Elliott PM, et al. Risk factors for malignant ventricular arrhythmias in lamin a/c mutation carriers a European cohort study. J Am Coll Cardiol 2012;59:493–500.
66. Bansch D, Antz M, Boczor S, Volkmer M, Tebbenjohanns J, Seidl K, Block M, Gietzen F, Berger J, Kuck KH. Primary prevention of sudden cardiac death in idiopathic dilated cardiomyopathy: the Cardiomyopathy Trial (CAT). Circulation 2002;105:1453–1458.
67. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004;350:2140–2150.
68. Desai AS, Fang JC, Maisel WH, Baughman KL. Implantable defibrillators for the prevention of mortality in patients with nonischemic cardiomyopathy: a meta-analysis of randomized controlled trials. JAMA 2004;292:2874–2879.
69. Kadish A, Dyer A, Daubert JP, et al. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. N Engl J Med 2004;350:2151–2158.
70. Strickberger SA, Hummel JD, Bartlett TG, Frumin HI, Schuger CD, Beau SL, Bitar C, Morady F, Investigators A. Amiodarone versus implantable cardioverter-defibrillator:randomized trial in patients with nonischemic dilated cardiomyopathy and asymptomatic nonsustained ventricular tachycardia–AMIOVIRT. J Am Coll Cardiol 2003;41:1707–1712.
71. Corrado D, Calkins H, Link MS, et al. Prophylactic implantable defibrillator in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia and no prior ventricular fibrillation or sustained ventricular tachycardia. Circulation 2010;122:1144–1152.
72. Mazzanti A, Ng K, Faragli A, et al. Arrhythmogenic Right Ventricular Cardiomyopathy: Clinical Course and Predictors of Arrhythmic Risk. J Am Coll Cardiol 2016;68:2540–2550.
73. Pinamonti B, Dragos AM, Pyxaras SA, Merlo M, Pivetta A, Barbati G, Di Lenarda A, Morgera T, Mestroni L, Sinagra G. Prognostic predictors in arrhythmogenic right ventricular cardiomyopathy: results from a 10-year registry. Eur Heart J 2011;32:1105–1113.
74. Anselme F, Moubarak G, Savoure A, Godin B, Borz B, Drouin-Garraud V, Gay A. Implantable cardioverter-defibrillators in lamin A/C mutation carriers with cardiac conduction disorders. Heart Rhythm 2013;10:1492–1498.
75. Kimura Y, Noda T, Otsuka Y, et al. Potentially Lethal Ventricular Arrhythmias and Heart Failure in Arrhythmogenic Right Ventricular Cardiomyopathy: What Are the Differences Between Men and Women? JACC Clin Electrophysiol 2016;2:546–555.
76. Pasotti M, Klersy C, Pilotto A, et al. Long-term outcome and risk stratification in dilated cardiolaminopathies. J Am Coll Cardiol 2008;52:1250–1260.
77. Wlodarska EK, Wozniak O, Konka M, Rydlewska-Sadowska W, Biederman A, Hoffman P. Thromboembolic complications in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy. Europace 2006;8:596–600.
78. Ruwald MH, Abu-Zeitone A, Jons C, Ruwald AC, McNitt S, Kutyifa V, Zareba W, Moss AJ. Impact of carvedilol and metoprolol on inappropriate implantable cardioverter-defibrillator therapy: the MADIT-CRT trial (Multicenter Automatic Defibrillator Implantation With Cardiac Resynchronization Therapy). J Am Coll Cardiol 2013;62:1343–1350.
79. Marcus GM, Glidden DV, Polonsky B, Zareba W, Smith LM, Cannom DS, Estes NA 3rd, Marcus F, Scheinman MM. Efficacy of antiarrhythmic drugs in arrhythmogenic right ventricular cardiomyopathy: a report from the North American ARVC Registry. J Am Coll Cardiol 2009;54:609–615.
80. Connolly SJ, Dorian P, Roberts RS, Gent M, Bailin S, Fain ES, Thorpe K, Champagne J, Talajic M, Coutu B, Gronefeld GC, Hohnloser SH. Comparison of beta-blockers, amiodarone plus beta-blockers, or sotalol for prevention of shocks from implantable cardioverter defibrillators: the OPTIC Study: a randomized trial. Jama 2006;295:165–171.
81. Ermakov S, Gerstenfeld EP, Svetlichnaya Y, Scheinman MM. Use of flecainide in combination antiarrhythmic therapy in patients with arrhythmogenic right ventricular cardiomyopathy. Heart Rhythm 2017;14:564–569.
82. Tokuda M, Tedrow UB, Kojodjojo P, Inada K, Koplan BA, Michaud GF, John RM, Epstein LM, Stevenson WG. Catheter ablation of ventricular tachycardia in nonischemic heart disease. Circ Arrhythm Electrophysiol 2012;5:992–1000.
83. Sapp JL, Wells GA, Parkash R, et al. Ventricular Tachycardia Ablation versus Escalation of Antiarrhythmic Drugs. N Engl J Med 2016;375:111–121.
84. Tung R, Vaseghi M, Frankel DS, et al. Freedom from recurrent ventricular tachycardia after catheter ablation is associated with improved survival in patients with structural heart disease: An International VT Ablation Center Collaborative Group study. Heart Rhythm 2015;12:1997–2007.
85. Tzou WS, Tung R, Frankel DS, et al. Outcomes after repeat ablation of ventricular tachycardia in structural heart disease: An analysis from the International VT Ablation Center Collaborative Group. Heart Rhythm 2017;14:991–997.
86. Santangeli P, Zado ES, Supple GE, Haqqani HM, Garcia FC, Tschabrunn CM, Callans DJ, Lin D, Dixit S, Hutchinson MD, Riley MP, Marchlinski FE. Long-Term Outcome With Catheter Ablation of Ventricular Tachycardia in Patients With Arrhythmogenic Right Ventricular Cardiomyopathy. Circ Arrhythm Electrophysiol 2015;8:1413–1421.
87. Mallidi J, Nadkarni GN, Berger RD, Calkins H, Nazarian S. Meta-analysis of catheter ablation as an adjunct to medical therapy for treatment of ventricular tachycardia in patients with structural heart disease. Heart Rhythm 2011;8:503–510.
88. Philips B, te Riele AS, Sawant A, Kareddy V, James CA, Murray B, Tichnell C, Kassamali B, Nazarian S, Judge DP, Calkins H, Tandri H. Outcomes and ventricular tachycardia recurrence characteristics after epicardial ablation of ventricular tachycardia in arrhythmogenic right ventricular dysplasia/cardiomyopathy. Heart Rhythm 2015;12:716–725.
89. Bai R, Di Biase L, Shivkumar K, et al. Ablation of ventricular arrhythmias in arrhythmogenic right ventricular dysplasia/cardiomyopathy: arrhythmia-free survival after endo-epicardial substrate based mapping and ablation. Circ Arrhythm Electrophysiol 2011;4:478–485.
90. Berruezo A, Acosta J, Fernandez-Armenta J, et al. Safety, long-term outcomes and predictors of recurrence after first-line combined endoepicardial ventricular tachycardia substrate ablation in arrhythmogenic cardiomyopathy. Impact of arrhythmic substrate distribution pattern. A prospective multicentre study. Europace 2017;19:607–616.
91. Dalal D, Jain R, Tandri H, et al. Long-term efficacy of catheter ablation of ventricular tachycardia in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy. J Am Coll Cardiol 2007;50:432–440.
92. Garcia FC, Bazan V, Zado ES, Ren JF, Marchlinski FE. Epicardial substrate and outcome with epicardial ablation of ventricular tachycardia in arrhythmogenic right ventricular cardiomyopathy/dysplasia. Circulation 2009;120:366–375.
93. Saberniak J, Hasselberg NE, Borgquist R, Platonov PG, Sarvari SI, Smith HJ, Ribe M, Holst AG, Edvardsen T, Haugaa KH. Vigorous physical activity impairs myocardial function in patients with arrhythmogenic right ventricular cardiomyopathy and in mutation positive family members. Eur J Heart Fail 2014;16:1337–1344.
94. James CA, Bhonsale A, Tichnell C, Murray B, Russell SD, Tandri H, Tedford RJ, Judge DP, Calkins H. Exercise increases age-related penetrance and arrhythmic risk in arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated desmosomal mutation carriers. J Am Coll Cardiol 2013;62:1290–1297.
95. Te Riele A, James CA, Sawant AC, et al. Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy in the Pediatric Population: Clinical Characterization

and Comparison With Adult-Onset Disease. JACC Clin Electrophysiol 2015; 1:551–560.
96. Sawant AC, Te Riele AS, Tichnell C, Murray B, Bhonsale A, Tandri H, Judge DP, Calkins H, James CA. Safety of American Heart Association-recommended minimum exercise for desmosomal mutation carriers. Heart Rhythm 2016;13:199–207.
97. Ruwald AC, Marcus F, Estes NA 3rd, Link M, McNitt S, Polonsky B, Calkins H, Towbin JA, Moss AJ, Zareba W. Association of competitive and recreational sport participation with cardiac events in patients with arrhythmogenic right ventricular cardiomyopathy: results from the North American multidisciplinary study of arrhythmogenic right ventricular cardiomyopathy. Eur Heart J 2015; 36:1735–1743.
98. Sen-Chowdhry S, Syrris P, Ward D, Asimaki A, Sevdalis E, McKenna WJ. Clinical and genetic characterization of families with arrhythmogenic right ventricular dysplasia/cardiomyopathy provides novel insights into patterns of disease expression. Circulation 2007;115:1710–1720.
99. Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett DR Jr, Tudor-Locke C, Greer JL, Vezina J, Whitt-Glover MC, Leon AS. 2011 Compendium of Physical Activities: a second update of codes and MET values. Med Sci Sports Exerc 2011;43:1575–1581.
100. Strath SJ, Kaminsky LA, Ainsworth BE, Ekelund U, Freedson PS, Gary RA, Richardson CR, Smith DT, Swartz AM. Guide to the assessment of physical activity: Clinical and research applications: a scientific statement from the American Heart Association. Circulation 2013;128:2259–2279.
101. Lie OH, Dejgaard LA, Saberniak J, Rootwelt C, Stokke MK, Edvardsen T, Haugaa KH. Harmful Effects of Exercise Intensity and Exercise Duration in Patients With Arrhythmogenic Cardiomyopathy. JACC Clin Electrophysiol 2018; 4:744–753.
102. Reisinger J, Dubrey SW, Lavalley M, Skinner M, Falk RH. Electrophysiologic abnormalities in AL (primary) amyloidosis with cardiac involvement. J Am Coll Cardiol 1997;30:1046–1051.
103. Eriksson A, Eriksson P, Olofsson BO, Thornell LE. The sinoatrial node in familial amyloidosis with polyneuropathy. A clinico-pathological study of nine cases from northern Sweden. Virchows Arch A Pathol Anat Histopathol 1984; 402:239–246.
104. Eriksson P, Olofsson BO. Pacemaker treatment in familial amyloidosis with polyneuropathy. Pacing Clin Electrophysiol 1984;7:702–706.
105. Sayed RH, Rogers D, Khan F, Wechalekar AD, Lachmann HJ, Fontana M, Mahmood S, Sachchithanantham S, Patel K, Hawkins PN, Whelan CJ, Gillmore JD. A study of implanted cardiac rhythm recorders in advanced cardiac AL amyloidosis. Eur Heart J 2015;36:1098–1105.
106. Muchtar E, Gertz MA, Kumar SK, et al. Digoxin use in systemic light-chain (AL) amyloidosis: contra-indicated or cautious use? Amyloid 2018;25:86–92.
107. Rezk T, Whelan CJ, Lachmann HJ, et al. Role of implantable intracardiac defibrillators in patients with cardiac immunoglobulin light chain amyloidosis. Br J Haematol 2018;182:145–148.
108. Tan NY, Mohsin Y, Hodge DO, Lacy MQ, Packer DL, Dispenzieri A, Grogan M, Asirvatham SJ, Madhavan M, Mc LC. Catheter Ablation for Atrial Arrhythmias in Patients With Cardiac Amyloidosis. J Cardiovasc Electrophysiol 2016;27:1167–1173.
109. Hoedemaekers YM, Caliskan K, Michels M, Frohn-Mulder I, van der Smagt JJ, Phefferkorn JE, Wessels MW, ten Cate FJ, Sijbrands EJ, Dooijes D, Majoor-Krakauer DF. The importance of genetic counseling, DNA diagnostics, and cardiologic family screening in left ventricular noncompaction cardiomyopathy. Circ Cardiovasc Genet 2010;3:232–239.
110. Muser D, Liang JJ, Witschey WR, et al. Ventricular arrhythmias associated with left ventricular noncompaction: Electrophysiologic characteristics, mapping, and ablation. Heart Rhythm 2017;14:166–175.
111. Miller EM, Hinton RB, Czosek R, Lorts A, Parrott A, Shikany AR, Ittenbach RF, Ware SM. Genetic Testing in Pediatric Left Ventricular Noncompaction. Circ Cardiovasc Genet 2017;10.
112. Caliskan K, Szili-Torok T, Theuns DA, Kardos A, Geleijnse ML, Balk AH, van Domburg RT, Jordaens L, Simoons ML. Indications and outcome of implantable cardioverter-defibrillators for primary and secondary prophylaxis in patients with noncompaction cardiomyopathy. J Cardiovasc Electrophysiol 2011; 22:898–904.
113. Stollberger C, Blazek G, Dobias C, Hanafin A, Wegner C, Finsterer J. Frequency of stroke and embolism in left ventricular hypertrabeculation/noncompaction. Am J Cardiol 2011;108:1021–1023.
114. Brescia ST, Rossano JW, Pignatelli R, Jefferies JL, Price JF, Decker JA, Denfield SW, Dreyer WJ, Smith O, Towbin JA, Kim JJ. Mortality and sudden death in pediatric left ventricular noncompaction in a tertiary referral center. Circulation 2013;127:2202–2208.
115. Kohli SK, Pantazis AA, Shah JS, Adeyemi B, Jackson G, McKenna WJ, Sharma S, Elliott PM. Diagnosis of left-ventricular non-compaction in patients with left-ventricular systolic dysfunction: time for a reappraisal of diagnostic criteria? Eur Heart J 2008;29:89–95.
116. Gleva MJ, Wang Y, Curtis JP, Berul CI, Huddleston CB, Poole JE. Complications Associated With Implantable Cardioverter Defibrillators in Adults With Congenital Heart Disease or Left Ventricular Noncompaction Cardiomyopathy (From the NCDR((R)) Implantable Cardioverter-Defibrillator Registry). Am J Cardiol 2017;120:1891–1898.
117. Gati S, Papadakis M, Papamichael ND, Zaidi A, Sheikh N, Reed M, Sharma R, Thilaganathan B, Sharma S. Reversible de novo left ventricular trabeculations in pregnant women: implications for the diagnosis of left ventricular noncompaction in low-risk populations. Circulation 2014;130:475–483.
118. Andreini D, Pontone G, Bogaert J, et al. Long-Term Prognostic Value of Cardiac Magnetic Resonance in Left Ventricle Noncompaction: A Prospective Multicenter Study. J Am Coll Cardiol 2016;68:2166–2181.
119. Ivanov A, Dabiesingh DS, Bhumireddy GP, Mohamed A, Asfour A, Briggs WM, Ho J, Khan SA, Grossman A, Klem I, Sacchi TJ, Heitner JF. Prevalence and Prognostic Significance of Left Ventricular Noncompaction in Patients Referred for Cardiac Magnetic Resonance Imaging. Circ Cardiovasc Imaging 2017;10.
120. Sidhu MS, Uthamalingam S, Ahmed W, Engel LC, Vorasettakarnkij Y, Lee AM, Hoffmann U, Brady T, Abbara S, Ghoshhajra BB. Defining left ventricular noncompaction using cardiac computed tomography. J Thorac Imaging 2014;29:60–66.
121. Chin TK, Perloff JK, Williams RG, Jue K, Mohrmann R. Isolated noncompaction of left ventricular myocardium. A study of eight cases. Circulation 1990; 82:507–513.
122. Jenni R, Oechslin E, Schneider J, Attenhofer Jost C, Kaufmann PA. Echocardiographic and pathoanatomical characteristics of isolated left ventricular noncompaction: a step towards classification as a distinct cardiomyopathy. Heart 2001;86:666–671.
123. Stollberger C, Finsterer J, Blazek G. Left ventricular hypertrabeculation/noncompaction and association with additional cardiac abnormalities and neuromuscular disorders. Am J Cardiol 2002;90:899–902.
124. Petersen SE, Selvanayagam JB, Wiesmann F, Robson MD, Francis JM, Anderson RH, Watkins H, Neubauer S. Left ventricular non-compaction: insights from cardiovascular magnetic resonance imaging. J Am Coll Cardiol 2005;46:101–105.
125. Thuny F, Jacquier A, Jop B, Giorgi R, Gaubert JY, Bartoli JM, Moulin G, Habib G. Assessment of left ventricular non-compaction in adults: side-by-side comparison of cardiac magnetic resonance imaging with echocardiography. Archives of cardiovascular diseases 2010;103:150–159.

Appendix 1 Author disclosure table

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
Jeffrey A. Towbin, MS, MD (Chair)	Le Bonheur Children's Hospital, Memphis, Tennessee; University of Tennessee Health Science Center, Memphis, Tennessee	None	None	None	None	None	None	None	None
William J. McKenna, MD, DSc (Vice-Chair)	University College London, Institute of Cardiovascular Science, London, United Kingdom	None	None	None	None	None	None	None	None
Dominic J. Abrams, MD, MRCP, MBA	Boston Children's Hospital, Boston, Massachusetts	1: Audentes Therapeutics	None	None	None	None	None	None	None
Michael J. Ackerman, MD, PhD	Mayo Clinic, Rochester, Minnesota	0: Abbott; 0: Audentes Therapeutics; 0: Boston Scientific; 0: Gilead Sciences; 0: MyoKardia; 1: Invitae; 1: Medtronic	None	5: NIH	None	None	None	0: AliveCor; 0: Blue 0x Healthcare; 0: StemoniX	None
Hugh Calkins, MD, FHRS, CCDS	Johns Hopkins University, Baltimore, Maryland	1: Abbott; 1: Biosense Webster; 1: Boston Scientific; 1: Sanofi Aventis; 1: Toray Industries; 2: Medtronic; 3: Boehringer Ingelheim	None	2: Boston Scientific	None	None	None	None	None
Francisco C.C. Darrieux, MD, PhD	Universidade de São Paulo, Instituto do Coração HCFMUSP, São Paulo, Brazil	1: Bayer; 1: Boehringer Ingelheim; 1: Daiichi-Sankyo; 1: Pfizer	None	None	None	None	None	None	None
James P. Daubert, MD, FHRS	Duke University Medical Center, Durham, North Carolina	1: Abbott; 1: ACC; 1: Biosense Webster; 1: Boston Scientific; 1: Iowa Approach; 1: LivaNova; 1: VytronUS; 1: ZOLL Medical Corporation; 2: Gilead Sciences; 2: Medtronic	None	0: Abbott; 0: Biosense Webster; 0: Boston Scientific; 0: Medtronic	3: Biosense Webster; 3: Boston Scientific; 3: Medtronic	None	None	None	None
Christian de Chillou, MD, PhD	Nancy University Hospital, Vandoeuvre-lès-Nancy, France	1: Abbott; 1: Biosense Webster; 1: Boston Scientific; 1: Medtronic	None	None	None	None	None	None	None

(*Continued*)

Appendix 1 (*Continued*)

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
Eugene C. DePasquale, MD	University of California, Los Angeles, Los Angeles, California	None	None	None	None	None	None	None	None
Milind Y. Desai, MD	Cleveland Clinic, Cleveland, Ohio	None	None	None	None	None	None	None	None
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
Wei Hua, MD, FHRS	Fu Wai Hospital, Beijing, China	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	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
Cynthia A. James, ScM, PhD, CGC	Johns Hopkins University, Baltimore, Maryland	1: Abbott	None	1: NSGC; 2: Boston Scientific	None	None	None	None	0: NSGC
Roy M. John, MBBS, PhD, CCDS, FHRS	Vanderbilt University Medical Center, Nashville, Tennessee	1: Abbott; Medtronic	None	None	None	None	None	None	None
Daniel P. Judge, MD	Medical University of South Carolina, Charleston, South Carolina	1: 4D Molecular Therapeutics; 1: Blade Therapeutics; 1: GlaxoSmithKline; 2: Pfizer	None	2: NIH; 1: Array BioPharma; 2: Eidos Biopharma	None	None	None	None	None
Roberto Keegan, MD	Hospital Privado Del Sur, Buenos Aires, Argentina, and Hospital Español, Bahia Blanca, Argentina	None	None	None	None	None	None	None	None
Andrew D. Krahn, MD, FHRS	The University of British Columbia, Vancouver, Canada	None	None	None	None	None	None	None	None
Mark S. Link, MD, FHRS	UT Southwestern Medical Center, Dallas, Texas	None	None	None	None	None	None	None	None
Frank I. Marcus, MD	University of Arizona, Sarver Heart Center, Tucson, Arizona	None	None	None	None	None	None	None	None

Christopher J. McLeod, MBChB, PhD, FHRS	Mayo Clinic, Rochester, Minnesota	None	None	None	None	None	None	None	None
Luisa Mestroni, MD	University of Colorado Anschutz Medical Campus, Aurora, Colorado	1: MyoKardia	None	4: AHA; 4: NIH; 5: Fondation Leducq	None	None	None	None	None
Silvia G. Priori, MD, PhD	University of Pavia, Pavia, Italy and European Reference Network for Rare and Low Prevalence Complex Diseases of the Heart; ICS Maugeri, IRCCS, Pavia, Italy	None	None	2: Cardurion	None	None	None	None	None
Jeffrey E. Saffitz, MD, PhD	Beth Israel Deaconess Medical Center, Boston, Massachusetts	None	None	None	None	None	None	None	None
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

(*Continued*)

Appendix 1 (*Continued*)

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
Wojciech Zareba, MD, PhD	University of Rochester, Rochester, New York	None	None	5: BIOTRONIK; 5: EBR Systems; 5: Gilead Sciences; 5: LivaNova	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.

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

*Research and fellowship support are classed as programmatic support. Sources of programmatic support are disclosed but are not regarded as a relevant relationship with industry for writing group members or reviewers.

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, *Circulation Arrhythmia and Electrophysiology*)
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, 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

(*Continued*)

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
Richard Hauer, MD	ICIN-Netherlands Heart Institute, Utrecht, the Netherlands	None	None	None	None	None	None	None	None
Minoru Horie, MD, PhD	Shiga University of Medical Sciences, Shiga, Japan	None	None	None	None	None	None	None	None
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
Kavita Sharma, MD	Johns Hopkins University, Baltimore, Maryland	1: Novartis Pharmaceuticals Corporation	None	3: NIH; 3: AHA	None	None	None	None	None
Yoshihide Takahashi, MD	Tokyo Medical and Dental University, Tokyo, Japan	1: Abbott; 1: Biosense Webster; 1: BIOTRONIK; 1: Japan Lifeline	None	None	None	None	None	None	None
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.

*Research and fellowship support are classed as programmatic support. Sources of programmatic support are disclosed but are not regarded as a relevant relationship with industry for writing group members or reviewers.