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

Executive summary

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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 and left ventricular noncompaction. The ACM phenotype presentation 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). For copies of this document, please contact the Elsevier Inc. Reprint Department (reprints@elsevier.com). Permissions: Multiple copies, modification, alteration, enhancement, and/or distribution of this document are not permitted without the express permission of the Heart Rhythm Society. Instructions for obtaining permission are located at https://www.elsevier.com/about/our-business/policies/copyright/permissions. Correspondence: Heart Rhythm Society, 1325 G Street NW, Suite 400, Washington, DC 20005. E-mail address: clinicaldocs@hrsonline.org.
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Section 1 Introduction

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

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

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
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>
<thead>
<tr>
<th>CLASS (STRENGTH) OF RECOMMENDATION</th>
<th>LEVEL (QUALITY) OF EVIDENCE‡</th>
</tr>
</thead>
</table>
| **CLASS I (STRONG)**  
Benefit >>> Risk  
Suggested phrases for writing recommendations:  
- Is recommended  
- Is indicated/useful/effective/beneficial  
- Should be performed/administered/other  
- Comparative-Effectiveness Phrases‡:  
  - Treatment/strategy A is recommended/indicated in preference to treatment B  
  - Treatment A should be chosen over treatment B |
| **LEVEL A** |
| - High-quality evidence‡ from more than 1 RCTs  
- Meta-analyses of high-quality RCTs  
- One or more RCTs corroborated by high-quality registry studies |
| **LEVEL B-R** (Randomized) |
| - Moderate-quality evidence‡ from 1 or more RCTs  
- Meta-analyses of moderate-quality RCTs |
| **LEVEL B-NR** (Nonrandomized) |
| - Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies  
- Meta-analyses of such studies |
| **LEVEL C-LD** (Limited Data) |
| - Randomized or nonrandomized observational or registry studies with limitations of design or execution  
- Meta-analyses of such studies  
- Physiological or mechanistic studies in human subjects |
| **LEVEL C-EO** (Expert Opinion) |
| - Consensus of expert opinion based on clinical experience |

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.‡

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

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

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

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

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

![Algorithm to consider the presence of an arrhythmogenic cardiomyopathy (ACM).](image-url)

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

**Arrhythmia includes conduction disease, atrial arrhythmias, ventricular arrhythmias
Ventricular Dysfunction in ACM
(not due to systemic disorders)

### Common Pathways

<table>
<thead>
<tr>
<th>Desmosome</th>
<th>Cytoskeleton</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercalated Disc</td>
<td>Sarcoplasmic Reticulum</td>
</tr>
<tr>
<td>Ion Channel</td>
<td>Sarcomere</td>
</tr>
<tr>
<td></td>
<td>Ion Channel</td>
</tr>
<tr>
<td></td>
<td>Mitochondria</td>
</tr>
</tbody>
</table>

### Genetic Variants

**PKP2, JUP**  
**DSC2, DSG2, DSP, SCN5A**  
**PLN**  
**LMNA, DSP, FLNC, TMEM43, LDB3, Desmin, α-actinin, BAG3, NKX2-5, RBM20, SCN5A, KCNQ1, KCNH2, TRPM4, Mitochondrial Mutations**

---

**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

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
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 Criteria

- **Global or regional dysfunction and structural alterations determined by echo, MRI, or RV angiography:**
  - Regional RV akinesia, dyskinesia, or aneurysm and 1 of the following (end diastole):
    - a) PLAX RVOT ≥32 mm (PLAX/BSA ≥21 mm/m²)
    - b) PSAX RVOT ≥36 mm (PSAX/BSA ≥21 mm/m²)
    - 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/m²)
    - b) PSAX RVOT ≥32 to <36 mm (PSAX/BSA ≥21 to <24 mm/m²)
    - c) Fractional area change >33 to ≤40%

### Minor Criteria

- **Regional RV akinesia or dyskinesia or dysynchronous RV contraction and 1 of the following:**
  - a) Ratio RVEDV/BSA ≥110 mL/m² (male), ≥100 mL/m² (female)
  - b) RVEF ≤40%
  - Regional RV akinesia or dyskinesia or dys synchronous RV contraction and 1 of the following:
    - a) Ratio RVEDV/BSA ≥100 to <110 mL/m² (male), ≥90 to 100 mL/m² (female)
    - b) RVEF >40 to 45%

### 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 (V1, V2, and V3) or beyond in individuals >14 years of age (in the absence of complete RBBB QRS ≥120ms)
  - I. Inverted T waves in leads V1, V2, and V3 or V4 in individuals >14 years of age (in the absence of complete RBBB)
  - II. Inverted T waves in leads V1, V2, and V3 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 (V1 to V3)
  - 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 5 wave to the end of the QRS, including R in V1, V2, or V3 in the absence of complete RBBB

#### Arrhythmias

- Non sustained or sustained VT of LBBB with superior axis (positive QRS in II, III, and aVF and positive in lead aVL)
  - I. Non sustained 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 pathogenic 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

3.2.2 Depolarization and conduction abnormalities

3.2.2.1 Prolonged terminal activation duration

Figure 7  Representative 12-lead electrocardiogram (ECG) obtained from patients with arrhythmogenic right ventricular cardiomyopathy (ARVC) with incomplete right bundle branch block (IRBBB) and complete right bundle branch block (CRBBB). QRS duration of IRBBB and CRBBB was 110 ms and 140 ms, respectively. The closed arrow indicates an epsilon wave, which was defined as low-amplitude deflection located between the end of the QRS and the onset of the T wave in leads V₁–V₃. The asterisk indicates the T wave inversion recorded in V₁–V₄ in patients with ARVC and IRBBB or CRBBB.

Figure 8  Terminal activation duration (TAD) is measured from the nadir of the S wave to the end of all depolarization deflections and is prolonged if ≥55 ms in any of the V₁–V₃ 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.
3.3 Genetic testing

### 3.3.1 Variant and gene interpretation

<table>
<thead>
<tr>
<th>Classification of likelihood of pathogenicity of a variant</th>
<th>Description</th>
<th>Likelihood of being pathogenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class 5 Pathogenic</td>
<td>NA</td>
<td>&gt;95%</td>
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<tr>
<td>Class 4 Likely pathogenic</td>
<td>NA</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>Class 3 Variant of uncertain significance</td>
<td>NT</td>
<td>10–90%</td>
</tr>
<tr>
<td>Class 2 Likely benign</td>
<td>NT or T</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>Class 1 Benign</td>
<td>NT or T</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>

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)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein type</th>
<th>Predominant type of mutation</th>
<th>OR/EF</th>
<th>Signal: background</th>
<th>Remarks</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAG3</td>
<td>Chaperone</td>
<td>Truncating and missense</td>
<td>NA</td>
<td>NA</td>
<td>Also causes myofibrillar myopathy</td>
<td>28</td>
</tr>
<tr>
<td>DES</td>
<td>IF</td>
<td>Truncating and missense</td>
<td>NA</td>
<td>NA</td>
<td>Also causes myofibrillar myopathy</td>
<td>29</td>
</tr>
<tr>
<td>DSC2</td>
<td>Desm</td>
<td>Truncating and missense</td>
<td>NT</td>
<td>ns</td>
<td>Rare</td>
<td>30</td>
</tr>
<tr>
<td>DSG2</td>
<td>Desm</td>
<td>Truncating and missense</td>
<td>NT</td>
<td>2:1* (NT/T)</td>
<td>Rarely recessive</td>
<td>31</td>
</tr>
<tr>
<td>DSP</td>
<td>Desm</td>
<td>Truncating and missense</td>
<td>NT</td>
<td>ns</td>
<td>Recessive: Carvajal syndrome</td>
<td>32,33</td>
</tr>
<tr>
<td>FLNC</td>
<td>Actin crosslink</td>
<td>Truncating and missense</td>
<td>NA</td>
<td>NA</td>
<td>Also causes myofibrillar myopathy</td>
<td>34</td>
</tr>
<tr>
<td>JUP</td>
<td>Desm</td>
<td>Missense</td>
<td>NT</td>
<td>10:1* (EF 1.0)</td>
<td>Large deletions 1-2%</td>
<td>40</td>
</tr>
<tr>
<td>LDB3</td>
<td>Z-band</td>
<td>Missense</td>
<td>NA</td>
<td>NA</td>
<td>Cypher/ZASP</td>
<td>35,36</td>
</tr>
<tr>
<td>LMNA</td>
<td>NE</td>
<td>Truncating and missense</td>
<td>NA</td>
<td>NA</td>
<td>AV block; CD</td>
<td>37</td>
</tr>
<tr>
<td>NKK2-5</td>
<td>Homeobox</td>
<td>Truncating and missense</td>
<td>NA</td>
<td>NA</td>
<td>AV block, CD, CHD</td>
<td>39</td>
</tr>
<tr>
<td>PKP2</td>
<td>Desm</td>
<td>Truncating</td>
<td>NT</td>
<td>42:1* (EF 1.0)</td>
<td>Large deletions 1-2%</td>
<td>40</td>
</tr>
<tr>
<td>PLN</td>
<td>Ca</td>
<td>Missense, nonsense, and deletion</td>
<td>NA</td>
<td>NA</td>
<td>Predominantly R14del</td>
<td>41,42</td>
</tr>
<tr>
<td>RBM20</td>
<td>Splice factor</td>
<td>Missense</td>
<td>NA</td>
<td>NA</td>
<td>Mostly in exon 9</td>
<td>43</td>
</tr>
<tr>
<td>SCN5A</td>
<td>Sodium channel</td>
<td>Mostly missense</td>
<td>NA</td>
<td>NA</td>
<td>Brugada, SND, CD</td>
<td>44</td>
</tr>
<tr>
<td>TMEM43</td>
<td>NE</td>
<td>Missense</td>
<td>NT</td>
<td>ns</td>
<td>p.5358L disease-causing; also called LUMA</td>
<td>45</td>
</tr>
</tbody>
</table>

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 = desmosoma; 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: ABCG9,18 TGFβ3,19 TN1,20 CTNNB1,11 sarcomeric genes (MYH7, MYBPC3),17,21 SCN3B,23 CDH2,24,25 TJP1.16
### 3.3.3 Advantages and disadvantages of various methods

| 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

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>C-E0</td>
<td>It is recommended that a genetic counselor or appropriately experienced clinician obtain a comprehensive 3-generation family history.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B-NR</td>
<td>It is recommended that first-degree relatives undergo clinical evaluation every 1–3 years starting at 10–12 years of age. Cardiovascular evaluation should include 12-lead ECG, ambulatory ECG, and cardiac imaging.</td>
</tr>
</tbody>
</table>

References:

34,47–52

46,51–57
3.4.3 Cascade cardiac investigations

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIb</td>
<td>C-LD</td>
<td>Exercise stress testing (arrhythmia provocation) may be considered as a useful adjunct to cardiovascular evaluation.</td>
<td>58</td>
</tr>
</tbody>
</table>

3.4.4 Cascade genetic testing

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIb</td>
<td>C-EO</td>
<td>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.</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>C-E0</td>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>B-NR</td>
<td>In individuals with ACM who have suffered a cardiac arrest with VT or VF, an ICD is recommended.</td>
<td>59–64</td>
</tr>
<tr>
<td>I</td>
<td>B-NR</td>
<td>In individuals with ACM who have sustained VT not hemodynamically tolerated, an ICD is recommended.</td>
<td>59–62,64</td>
</tr>
<tr>
<td>I</td>
<td>B-NR</td>
<td>In individuals with ACM (other than ARVC) and hemodynamically tolerated VT, an ICD is recommended.</td>
<td>50,65</td>
</tr>
<tr>
<td>I</td>
<td>B-R</td>
<td>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.</td>
<td>64,66–70</td>
</tr>
<tr>
<td>IIa</td>
<td>B-R</td>
<td>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.</td>
<td>69</td>
</tr>
<tr>
<td>IIa</td>
<td>B-NR</td>
<td>In individuals with ACM and syncope suspected to be due to a ventricular arrhythmia, an ICD is reasonable.</td>
<td>59–62,66,68–74</td>
</tr>
<tr>
<td>IIa</td>
<td>B-NR</td>
<td>In individuals with ARVC with hemodynamically tolerated sustained VT, an ICD is reasonable.</td>
<td>60–62,72</td>
</tr>
<tr>
<td>IIa</td>
<td>B-NR</td>
<td>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.*</td>
<td>61,62,72,75</td>
</tr>
<tr>
<td>IIa</td>
<td>B-NR</td>
<td>In individuals with phospholamban cardiomyopathy and LVEF &lt;45% or NSVT, an ICD is reasonable.</td>
<td>50</td>
</tr>
<tr>
<td>IIa</td>
<td>B-NR</td>
<td>In individuals with lamin A/C ACM and two or more of the following: LVEF &lt;45%, NSVT, male sex, an ICD is reasonable.</td>
<td>65</td>
</tr>
<tr>
<td>IIa</td>
<td>C-LD</td>
<td>In individuals with lamin A/C ACM and an indication for pacing, an ICD with pacing capabilities is reasonable.</td>
<td>49,74,76</td>
</tr>
<tr>
<td>IIa</td>
<td>C-LD</td>
<td>In individuals with FLNC ACM and an LVEF &lt;45%, an ICD is reasonable.</td>
<td>34</td>
</tr>
<tr>
<td>IIb</td>
<td>B-NR</td>
<td>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.*</td>
<td>61,62,72,75</td>
</tr>
</tbody>
</table>

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

Cardiac arrest or sustained VT not hemodynamically tolerated?

- Yes
  - In individuals with ACM who have sustained VT not hemodynamically tolerated, an ICD is recommended (COR I, LOE B-NR).

- No
  - In individuals with ACM who have suffered a cardiac arrest with VT or VF, an ICD is recommended (COR I, LOE B-NR).

Hemodynamically tolerated sustained VT or syncope suspected due to ventricular arrhythmia?

- Yes
  - In individuals with ACM and syncope suspected to be due to a ventricular arrhythmia, an ICD is reasonable (COR IIa, LOE B-NR).
  - In individuals with phospholamban cardiomyopathy and LVEF <45% or NSVT, an ICD is reasonable (COR IIa, LOE B-NR).

- No
  - In individuals with ARVC with hemodynamically tolerated sustained VT, an ICD is reasonable (COR IIa, LOE 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 (COR IIa, LOE B-NR).

Phospholamban, FLNC mutation, or lamin A/C ACM with LVEF <45%?

- Yes
  - In individuals with phospholamban cardiomyopathy and LVEF <45% or NSVT, an ICD is reasonable (COR IIa, LOE B-NR).

- No
  - In individuals with ARVC with hemodynamically tolerated sustained VT, an ICD is reasonable (COR IIa, LOE B-NR).
  - In individuals with lamin A/C ACM and an indication for pacing, an ICD with pacing capabilities is reasonable (COR IIa, LOE C-LD).

LVEF ≤35%?

- Yes
  - 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 (COR I, LOE 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 (COR IIa, LOE B-R).

- No
  - In individuals with ARVC with hemodynamically tolerated sustained VT, an ICD is reasonable (COR IIa, LOE B-NR).
  - In individuals with lamin A/C ACM and an LVEF <45%, an ICD is reasonable (COR IIa, LOE C-LD).

Major and minor criteria present?*

- Yes
  - ICD implantation may be reasonable for individuals with ARVC and three major, two major and two minor, or one major and four minor risk factors for ventricular arrhythmia* (COR IIb, LOE B-NR).

- No
  - 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* (COR IIb, LOE B-NR).

*Major criteria: NSVT, inducibility to VT at EPS, LVEF ≤49%, Minor criteria: male sex, >1000 PVCs/24 h, right ventricular dysfunction (as per major criteria of the 2010 Task Force Criteria), proband status, two 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

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
</table>
| IIa  | C-E0 | In individuals with ACM and symptomatic RV dysfunction, the use of ACE inhibitors or ar
giosin receptor blockers (ARBs), as well as beta-blockers, aldosterone antagonists, and diuretics is reasonable. |
| IIb  | C-E0 | 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

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B-NR</td>
<td>In individuals with ACM, in the presence of atrial fibrillation, intracavitary thrombosis, or venous/systemic thromboembolism, anticoagulant therapy is recommended.</td>
</tr>
<tr>
<td>IIb</td>
<td>C-E0</td>
<td>Antithrombotic therapy may be reasonable in individuals with LV or RV aneurysm.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>C-LD</td>
<td>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.</td>
<td>78</td>
</tr>
<tr>
<td>IIa</td>
<td>C-EO</td>
<td>Beta-blocker therapy is reasonable in individuals with ACM who do not have an ICD.</td>
<td></td>
</tr>
<tr>
<td>IIb</td>
<td>B-NR</td>
<td>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.</td>
<td>72,79,80</td>
</tr>
<tr>
<td></td>
<td>C-LD</td>
<td>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.</td>
<td>81</td>
</tr>
</tbody>
</table>

**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

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

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

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

3.7.1 Exercise and other arrhythmogenic cardiomyopathies

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B-NR</td>
<td>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.</td>
<td>93–96</td>
</tr>
<tr>
<td>III: Harm</td>
<td>B-NR</td>
<td>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.</td>
<td>72,93–98</td>
</tr>
</tbody>
</table>

**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.
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 activities99 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](image)

**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).
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.

In individuals with cardiac amyloidosis who have survived a cardiac arrest, an ICD is recommended if meaningful survival greater than 1 year is expected.

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.

In individuals with cardiac amyloidosis and symptomatic atrial arrhythmias, cardiac ablation may be considered.

In individuals with cardiac amyloidosis and symptomatic atrial arrhythmias, the use of sotalol, dofetilide, or amiodarone may be considered.

In individuals with cardiac amyloidosis and symptomatic atrial arrhythmias, the use of digoxin may be considered if used with caution due to the high risk of toxicity.

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

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B-NR</td>
<td>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.</td>
<td>109–111</td>
</tr>
<tr>
<td>I</td>
<td>B-NR</td>
<td>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.</td>
<td>112</td>
</tr>
<tr>
<td>I</td>
<td>B-NR</td>
<td>Anticoagulation is recommended in individuals with LVNC with atrial fibrillation and in those with previous embolic events.</td>
<td>113</td>
</tr>
<tr>
<td>IIa</td>
<td>B-NR</td>
<td>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.</td>
<td>109,111</td>
</tr>
<tr>
<td>IIa</td>
<td>B-NR</td>
<td>ICD implantation is reasonable in individuals with LVNC and evidence of nonsustained VT associated with a reduced ejection fraction.</td>
<td>112,114</td>
</tr>
<tr>
<td>IIb</td>
<td>B-NR</td>
<td>Anticoagulation may be reasonable in individuals with LVNC with evidence of ventricular dysfunction.</td>
<td>113</td>
</tr>
<tr>
<td>IIb</td>
<td>B-NR</td>
<td>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.</td>
<td>115–119</td>
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<td>IIb</td>
<td>B-NR</td>
<td>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.</td>
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Table 5  Diagnostic criteria for left ventricular noncompaction (LVNC)

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<tr>
<td>121</td>
<td>Echo</td>
<td>8</td>
<td>2 layers, excessively prominent ventricular trabeculations, progressively increased total myocardial wall thickness from mitral valve and towards the apex, CM/(NC + CM) ≤0.5 at end-diastole (short-axis parasternal and/or apical views)</td>
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<tr>
<td>122</td>
<td>Echo</td>
<td>34</td>
<td>2 layers, intertrabecular recesses by CFD, no co-existing structural abnormality, NC/C layer ≥2</td>
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<td>123</td>
<td>Echo</td>
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<td>&gt;3 trabeculations protruding from LV wall apically to papillary muscle. End-diastolic NC/C layer ≥2</td>
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<tr>
<td>124</td>
<td>MRI</td>
<td>7</td>
<td>2 layers. End-diastolic NC/C &gt;2.3</td>
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<tr>
<td>125</td>
<td>MRI</td>
<td>16</td>
<td>Total LV trabeculated mass without papillary muscles. End-diastolic NC layer volume &gt;20%</td>
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C = compaction; CM = compacted myocardium; echo = echocardiogram; LV = left ventricle; MRI = magnetic resonance imaging; NC/C = maximum noncompaction to compaction ratio; NCM = noncompacted myocardium.
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 (COR IIa, LOE 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 (COR I, LOE 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 (COR IIb, LOE B-NR).

In individuals with suspected LVNC, the diagnostic criteria by echocardiography or CMR, measured as the maximal ratio of noncompaction to compaction (NC/C), may be reasonable for establishing a diagnosis (COR IIb, LOE B-NR).

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.
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.

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<td>Stuart Dean Russell, MD</td>
<td>Duke University School of Medicine, Durham, North Carolina</td>
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<td>0: Abbott Laboratories; 0: SubQ Pharmaceuticals</td>
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<td>Frederic Sacher, MD, PhD</td>
<td>LIRYC Institute/University of Bordeaux, Pessac, France</td>
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<td>Mauricio Scanavacca, MD</td>
<td>Instituto do Coração, São Paulo, Brazil</td>
<td>1: Novartis Pharmaceuticals Corporation</td>
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<td>Kavita Sharma, MD</td>
<td>Johns Hopkins University, Baltimore, Maryland</td>
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<td>Yoshihide Takahashi, MD</td>
<td>Tokyo Medical and Dental University, Tokyo, Japan</td>
<td>1: Abbott; 1: Biosense Webster; 1: BIOTRONIK; 1: Japan Lifeline</td>
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<td>Harikrishna Tandri, MBBS, MD</td>
<td>Johns Hopkins University, Baltimore, Maryland</td>
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<tr>
<td>Gaurav A. Upadhyay, MD, FACC</td>
<td>University of Chicago Medicine, Chicago, Illinois</td>
<td>1: Abbott; 1: BIOTRONIK; 1: CardioNet; 1: Medtronic; 1: ZOLL Medical Corporation</td>
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<tr>
<td>Christian Wolpert, MD</td>
<td>University Hospital Mannheim, Ludwigsburg, Germany</td>
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Number value: 0 = $0; 1 = $10,000 to $25,000; 2 = $25,000 to $50,000; 3 = $50,000 to $100,000; 5 = $100,000.

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

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