

Diagnostic and therapeutic strategies for arrhythmogenic right ventricular dysplasia/cardiomyopathy patient

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Received 15 December 2017; editorial decision 11 March 2018; accepted 16 March 2018; online publish-ahead-of-print 23 April 2018

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is a rare inherited heart muscle disease characterized by ventricular tachyarrhythmia, predominant right ventricular dysfunction, and sudden cardiac death. Its pathophysiology involves close interaction between genetic mutations and exposure to physical activity. Mutations in genes encoding desmosomal protein are the most common genetic basis. Genetic testing plays important roles in diagnosis and screening of family members. Syncope, palpitation, and lightheadedness are the most common symptoms. The 2010 Task Force Criteria is the standard for diagnosis today. Implantation of a defibrillator in high-risk patients is the only therapy that provides adequate protection against sudden death. Selection of patients who are best candidates for defibrillator implantation is challenging. Exercise restriction is critical in affected individuals and at-risk family members. Antiarrhythmic drugs and ventricular tachycardia ablation are valuable but palliative components of the management. This review focuses on the current diagnostic and therapeutic strategies in ARVD/C and outlines the future area of development in this field.

Keywords

Arrhythmogenic right ventricular dysplasia/cardiomyopathy • Genetic • Antiarrhythmic drugs • Implantable cardioverter-defibrillators • Ventricular tachycardia • Sudden cardiac death

Introduction

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is an inherited heart muscle disease characterized by ventricular arrhythmias, an increased risk of sudden death, and predominant right ventricular dysfunction.¹ The pathological hallmark of ARVD/C is myocyte loss with fibro-fatty production. Since the first case series in 1982,^{2–4} our understanding of its pathogenesis, clinical manifestations, and long-term outcomes has advanced significantly. Arrhythmogenic right ventricular dysplasia/cardiomyopathy was initially considered to be a congenital defect in the right ventricular myocardium and designated as dysplasia but later was reclassified as a cardiomyopathy.⁵ While involvement of the right ventricle typically predominates in early disease, biventricular, and left dominant forms are now recognized to be an important part of the disease spectrum.⁶ The purpose of this review article is to provide an update concerning the diagnosis and treatment strategies in ARVD/C.

Epidemiology

Arrhythmogenic right ventricular dysplasia/cardiomyopathy is a rare condition⁷ and has an estimated prevalence of 1:5000.⁸ Arrhythmogenic right ventricular dysplasia/cardiomyopathy patients typically present in the 2nd to 4th decade of life.^{9–11} Approximately 20% of the patients present after age of 50 years. Late presentation does not confer a benign prognosis.¹² Men are more commonly affected with earlier onset than women and have worse outcomes once diagnosed.^{13–15} This may be explained by sex-related difference in hormone profiles and exercise participation.^{16,17}

Genetic basis

Arrhythmogenic right ventricular dysplasia/cardiomyopathy is mainly inherited in an autosomal-dominant pattern with incomplete

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penetrance and variable expressivity.¹⁸ Autosomal recessive forms have also been described and can be associated with woolly hair and palmoplantar keratoderma, such as in Naxos disease and Carvajal syndrome.¹⁹

The discovery of the genetic basis of Naxos disease identified the first disease-causing gene²⁰ in ARVD/C. It is located at chromosome 17q21 and encodes plakoglobin (*JUP*), a desmosomal protein important in cell-to-cell adhesion. This was followed by the discovery of mutations in genes that encode other desmosomal proteins including desmoplakin (*DSP*),²¹ plakophilin-2 (*PKP2*),²² desmoglein-2 (*DSG2*),^{23,24} and desmocollin-2 (*DSC2*),²⁵ all of which cause autosomal-dominant forms of ARVD/C.

Mutations in genes encoding non-desmosomal proteins have also been identified. Most are associated with other cardiomyopathies and arrhythmia syndrome and represent phenotypic overlap. These include the intermediate filament protein desmin (*DES*),²⁶ the cardiac sodium channel—Na_v 1.5 (*SCN5A*),²⁷ lamin A/C (*LMNA*)²⁸ on the nuclear membrane, titin (*TTN*),²⁹ phospholamban (*PLN*),³⁰ and filamin C (*FLNC*).³¹ Pathogenic variants in genes encoding proteins of the area composita, α -T-Catenin (*CTNNA3*),³² and N-cadherin (*CDH2*),³³ have been identified in a small group of ARVD/C patients with typical right-predominant disease. The pS358L founder mutation in *TMEM43*, encoding transmembrane protein 43 is common among French Canadian ARVD/C patients.⁹ Possible mutations in transforming growth factor beta-3 (*TGFB3*)³⁴ have been described but association with ARVD/C remains to be confirmed.

Among all the index cases, *PKP2* is the most commonly mutated gene (20–46%), followed by *DSP* (3–15%), *DSG2* (3–20%), *DSC2* (1–8%), and *JUP* (<1%).^{35,36} Non-desmosomal genes account for less than 10% of all pathological variants.³⁵

Attempts have been made to correlate genotypes to phenotypes. Patients with more than 1 mutation (4–16%) have earlier disease onset and worse disease outcomes including arrhythmia, sudden cardiac death, and heart failure.^{37,38} As in Carvajal syndrome, *DSP* mutations are also associated with left ventricular dysfunction, sometimes referred to as arrhythmogenic left ventricular dysplasia.^{37,39} Table 1 provides a list of the genes for which ARVD/C-associated disease-causing mutations have been identified. Novel mutations can be found and registered at www.ARVD/Cdatabase.info.⁴¹

Pathophysiology

Arrhythmogenic right ventricular dysplasia/cardiomyopathy is hypothesized as a disease of desmosomal dysfunction based on its genetics. This is supported by the remodelling of intercalated disk⁴² and loss of desmosomes observed in ultra-structural studies.⁴³ Desmosomes and gap junctions are responsible for maintaining cell adhesion, signal transduction, and electrical integrity, all of which have been implicated in the disease pathophysiology.

Defective desmosomal proteins lead to loss of adhesion between cardiac myocytes followed by inflammation, fibrosis, death, and production by fibrofatty tissue.²⁰ This may be aggravated by wall stress from physical activity which disproportionately affects right ventricle compared with left ventricle.⁴⁴

Besides providing mechanical cell adhesion, desmosomes are also important in intracellular and intercellular signal transduction.^{45,46}

Table 1 Genes where mutations are identified to cause arrhythmogenic right ventricular dysplasia/cardiomyopathy

Gene	Protein encoded	% cases ³⁶
<i>PKP2</i> ²²	Plakophilin-2	20–46
<i>DSP</i> ²¹	Desmoplakin	3–15
<i>DSG2</i> ^{23,24}	Desmoglein-2	3–20
<i>DSC2</i> ²⁵	Desmocollin-2	1–8
<i>JUP</i> ²⁰	Plakoglobin	<1
<i>CTNNA3</i> ³²	α -T-Catenin	<2
<i>CDH2</i> ³³	N-cadherin	<2
<i>TMEM43</i> ⁴⁰	Transmembrane protein 43	<2
<i>LMNA</i> ²⁸	Lamin A/C	<4
<i>SCN5A</i> ²⁷	Na _v 1.5	2
<i>DES</i> ²⁶	Desmin	<2
<i>PLN</i> ³⁰	Phospholamban	<1
<i>TTN</i> ²⁹	Titin	<10

Desmosomal alteration redistributes plakoglobin from cell surface to cytosol and nucleus, which suppresses canonical Wnt signalling by competing with β -catenin.⁴⁷ It promotes adipogenesis in the heart by increasing adipogenic factors and reducing inhibitors of adipogenesis, which may explain the typical fibroadipocytic production in ARVD/C.^{48,49} Lipogenesis and apoptosis have been reproduced by induction of adult-like metabolism in an *in vitro* model generated by patient-specific mutant *PKP2* induced pluripotent stem cells-derived cardiomyocytes.⁵⁰ Apart from protein relocation, epitope masking has also been reported to cause reduced plakoglobin immunoreactivity in intercalated discs.⁵¹

Desmosomes also maintain electrical integrity by forming a coordinated protein network called ‘connexome’ at the intercalated disks by interacting with ion channels and gap junctions.^{52,53} Disruption of electrical coupling may explain the increased arrhythmia susceptibility in ARVD/C even before the onset of significant fibrosis and necrosis.⁵⁴ The aggregation of voltage-gated sodium channels with cell adhesion molecules and reduced sodium current from desmosomal mutations may explain the phenotypic overlapping between ARVD/C and Brugada syndrome.^{55,56} Clinically, both conditions can manifest as right precordial electrocardiography (ECG) repolarization abnormalities, right ventricular outflow tract (RVOT) conduction disturbances, and ventricular arrhythmias the from right ventricle.⁵⁷ Pathologically, fatty infiltration of the myocardium has been reported in both conditions.^{58,59} As a result, ARVD/C and Brugada syndrome might be at the ends of a spectrum of structural myopathies and sodium current deficiency that share a common origin from abnormal connexome.⁵⁶

Exercise has been shown to exacerbate phenotypes in mice with ARVD/C associated mutations.^{60,61} In clinical studies, exercise is associated with disease penetrance and ventricular arrhythmia in ARVD/C.^{17,62,63} On a population level, ARVD/C has also been reported as a leading cause of sudden cardiac death in competitive athletes.^{64,65}

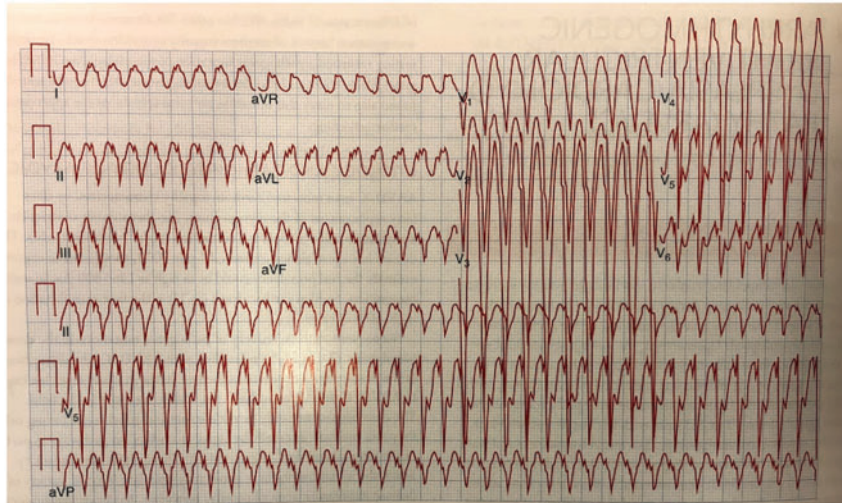


Figure 1 Ventricular tachycardia on a 12-lead electrocardiogram, which occurred in an ARVD/C patients. The VT morphology is left bundle branch block, superior axis. ARVD/C, arrhythmogenic right ventricular dysplasia/cardiomyopathy; VT, ventricular tachycardia.

Clinical manifestations

The presentation of ARVD/C varies considerably, ranging from proband patients with symptoms related to arrhythmia and heart failure to asymptomatic family members diagnosed in the context of cascade screening. Based on experience from referral centres, index patients usually present with palpitations (30–60%), lightheadedness (20%), and syncope (10–30%).^{7,13,18,66,67} These symptoms are in turn linked to the presence of non-sustained or sustained ventricular arrhythmias. Up to 19% of ARVD/C patients present as cardiac arrest.⁶⁸ Arrhythmogenic right ventricular dysplasia/cardiomyopathy can occasionally manifest as chest pain accompanied by transient ischaemic electrocardiographic changes and troponin elevation, mimicking acute myocarditis and heart attack.⁶⁹ Atypical chest pain may be explained by small vessel disease producing spasm.⁷⁰ Although not at the origin of the disease, myocarditis is thought to be a superimposed phenomenon^{71,72} and certain mutations may increase the susceptibility to it in ARVD/C.³⁹

Three stages have been described in the natural history of ARVD/C.^{5,73} In the initial ‘concealed stage’, individuals are asymptomatic. There are no or subtle structural changes in the right ventricle. The risk of cardiac arrest occurring in the concealed phase is extremely small but not zero. About 60% of the cardiac arrest victims were asymptomatic before their event.⁶⁸ As the disease progresses into the ‘clinically overt stage’, symptoms emerge as ventricular arrhythmias and morphological abnormalities in the right ventricle appear. Ventricular arrhythmias range from premature ventricular complexes, non-sustained or sustained ventricular tachycardia, and ventricular fibrillation¹⁸ (Figure 1). Atrial arrhythmias and atrial fibrillation have also been associated with ARVD/C.^{74–77} Haemodynamically tolerated ventricular tachycardia has been found in up to 60% of the index patients in their initial presentation.⁷⁸ In a subset of patients, the disease may progress to right, left, or biventricular failure. We recently reported that 49% of ARVD/C patients had at least one heart failure symptom,

with exertional dyspnoea being more common than volume overload. Among ARVD/C patients with heart failure, approximately 80% have isolated right ventricular dysfunction. Female sex and lateral precordial T-wave inversions have been associated with heart failure.⁷⁹ According to experience at Johns Hopkins and the Nordic ARVD/C Registry, heart failure is the most common (90%) indication to heart transplant in ARVD/C⁸⁰ and age at first symptoms under 35 years predicts transplantation.⁸¹ Among patients undergoing heart transplant, 58% had biventricular failure, 29% had right ventricular failure, and 3% had left ventricular failure. Sudden cardiac death also occurs at the end of the disease from overt heart failure.

Diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy

2010 Task Force Criteria

Arrhythmogenic right ventricular dysplasia/cardiomyopathy is a clinical diagnosis with no single gold-standard test. The 2010 Task Force Criteria (TFC) is the standard for diagnosis today⁸² (Table 2). It is a scoring system combining the six categories of disease features: right ventricular structural alteration, tissue characterization, repolarization abnormalities, depolarization abnormalities, arrhythmias, and family history. In each category, a major, minor, or no criterion can be met. Definite ARVD/C is diagnosed if an individual has at least ‘four points’ with a major criterion worth two points and one minor worth one point. A score of ‘three points’ is classified as probable ARVD/C. The criteria must come from different categories. The 2010 TFC is revised from the 1994 international task force guideline⁸³ with the addition of quantitative criteria of structural alterations and genetic testing. Its application has reduced the number of individuals satisfying the imaging criterion, increased the number of family

Table 2 2010 Task Force Criteria diagnostic criteria for ARVD/C

I. Global/regional dysfunction/structural alterations	
Major	By 2D echo <ul style="list-style-type: none"> Regional RV akinesia, dyskinesia, or aneurysm And one of the following (end diastole) <ul style="list-style-type: none"> PLAX RVOT ≥ 32 mm (correct for body size) [PLAX/BSA] ≥ 19 mm/m² PSAX RVOT ≥ 36 mm (correct for body size) [PSAX/BSA] ≥ 21 mm/m² Or fractional area change $\leq 33\%$ By MRI <ul style="list-style-type: none"> Regional RV akinesia or dyskinesia or dyssynchronous RV contraction And one of the following <ul style="list-style-type: none"> Ratio of RV end-diastolic volume to BSA ≥ 110 mL/m² (male) or ≥ 100 mL/m² (female) Or RV ejection fraction $\leq 40\%$ By RV angiography <ul style="list-style-type: none"> Regional RV akinesia, dyskinesia, or aneurysm
Minor	By 2D echo <ul style="list-style-type: none"> Regional RV akinesia or dyskinesia And one of the following (end diastole) <ul style="list-style-type: none"> PLAX RVOT ≥ 29 to < 32 mm (correct body size) [PLAX/BSA] ≥ 16 to < 19 mm/m² PSAX RVOT ≥ 32 to < 36 mm (correct body size) [PSAX/BSA] ≥ 18 to < 21 mm/m² Or fractional area change $> 33\%$ to $\leq 40\%$ By MRI <ul style="list-style-type: none"> Regional RV akinesia or dyskinesia or dyssynchronous RV contraction And one of the following <ul style="list-style-type: none"> Ratio of RVEDV to BSA ≥ 100 to < 110 mL/m² (male) or ≥ 90 to < 100 mL/m² (female) Or RV ejection fraction $> 40\%$ to $\leq 45\%$
II. Tissue characterization of wall	
Major	<ul style="list-style-type: none"> Residual myocytes $< 60\%$ by morphometric analysis (or $< 50\%$ if estimated), with fibrosis replacement of RV free wall myocardium in ≥ 1 sample, with or without fatty replacement of tissue on endomyocardial biopsy
Minor	<ul style="list-style-type: none"> Residual myocytes 60–75% by morphometric analysis (or 50–60% if estimated) with fibrous replacement of the RV free wall in ≥ 1 sample, with or without fatty replacement of tissue on endomyocardial biopsy
III. Repolarization abnormalities	
Major	<ul style="list-style-type: none"> T-wave inversions (V_1, V_2, V_3) or beyond; > 14 years; in absence of complete right bundle branch block QRS ≥ 120 ms
Minor	<ul style="list-style-type: none"> T-wave inversions in V_1 and V_2; > 14 years; in absence of complete right bundle branch block or in V_4, V_5, or V_6 T-wave inversions in V_1–V_4; > 14 years; in presence of complete right bundle branch block

Continued

Table 2 Continued

IV. Depolarization/conduction abnormalities	
Major	<ul style="list-style-type: none"> Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of T wave) in right precordial leads (V_1–V_3)
Minor	<ul style="list-style-type: none"> Late potentials by SAECC in ≥ 1 of 3 parameters in absence of QRS duration of ≥ 110 ms on ECG <ul style="list-style-type: none"> Filtered QRS duration (fQRS) ≥ 114 ms Duration of terminal QRS < 40 μV (low-amplitude signal duration) ≥ 38 ms Root mean square voltage of terminal 40 ms ≤ 20 μV Terminal activation duration of QRS ≥ 55 ms measured from nadir of S wave to end of QRS, including R', in V_1, V_2, or V_3, in absence of complete right bundle branch block
V. Arrhythmias	
Major	<ul style="list-style-type: none"> Non-sustained or sustained ventricular tachycardia of left bundle-branch morphology with superior axis (negative or indeterminate QRS in II, III, and aVF and positive in aVL)
Minor	<ul style="list-style-type: none"> Non-sustained or sustained ventricular tachycardia of RV outflow configuration, left bundle-branch morphology with inferior axis (positive QRS in II, III, and aVF and negative in aVL) or of unknown axis > 500 ventricular extrasystoles per 24 h (Holter)
VI. Family history	
Major	<ul style="list-style-type: none"> ARVC confirmed in first-degree relative who meets current TFC ARVC confirmed pathologically at autopsy or surgery in first-degree relative Pathogenic mutation (associated or probably associated with ARVC) in patient under evaluation
Minor	<ul style="list-style-type: none"> Hx of ARVC in first-degree relative in whom not possible or practical to determine if family member meets TFC Premature sudden death (< 35 years) due to suspected ARVC in first-degree relative ARVC confirmed pathologically or by current TFC in second-degree relative

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Definite = 2 major OR 1 major + 2 minor/Borderline = 1 major + 1 minor OR 3 minor/Possible = 1 major OR 2 minor.

ARVD/C, arrhythmogenic right ventricular dysplasia/cardiomyopathy; aVF, augmented voltage unipolar left foot lead; aVL, augmented voltage unipolar left arm lead; BSA, body surface area; ECG, electrocardiogram; MRI, magnetic resonance imaging; PLAX, parasternal long-axis view; PSAX, parasternal short-axis view; RV, right ventricle; RVEDV, right ventricular end diastolic volume; RVOT, right ventricular outflow tract; SAECC, signal-averaged electrocardiogram; TFC, Task Force Criteria.

members being diagnosed, and increased the overall diagnostic yield of ARVD/C compared with its 1994 counterpart.^{84,85} Although being the current gold standard, the 2010 TFC do not apply to left-dominant forms,⁶ which will likely be included in future revisions.⁸⁶

General diagnostic approach

When ARVD/C is suspected, the initial evaluation should include clinical inquiry about symptoms related to arrhythmia and heart failure, a detailed multi-generation family history, an exercise history, 12-lead ECG, ambulatory Holter monitoring, echocardiography, and cardiac magnetic resonance imaging (CMR). If the diagnosis remains inconclusive after this non-invasive approach, electrophysiological testing can be considered to characterize the arrhythmic substrate and stratify arrhythmic risk.^{87,88} Endomyocardial biopsy is rarely performed because of its invasiveness and poor sensitivity and specificity. Right ventriculography has been largely replaced by the echocardiography and CMR. Genetic testing is indicated for index patients with unequivocal phenotype and cascade screening of family members.⁸⁹

Electrocardiography

The standard 12-lead ECG is rarely normal in ARVD/C patients.⁹⁰ It provides critical clues of the depolarization and repolarization abnormalities in ARVD/C. T-wave inversion from V1 to V3 in the absence of complete right bundle branch block is a major TFC criterion and the most common ECG finding^{9,91} (Figure 2). T-wave inversion in V1 and V2 is a minor criterion.⁸² Negative T waves may extend to V5 and V6, indicating severe structural abnormality and left-sided involvement.⁹² Incomplete right bundle branch block is seen in 15% of ARVD/C patients and T-wave inversions through V3 maintains optimal sensitivity and specificity in its presence. In the presence of complete right bundle branch block, the most sensitive and specific diagnostic parameter is an *r/s* ratio <1.⁹¹ It is important to recognize that the left dominant form of ARVD/C has a different ECG pattern than the more common right dominant form. Inverted T-waves can be confined to the (infero) lateral leads in left dominant form of ARVD/C.⁹³ Low precordial QRS voltage may be seen but are not included in the TFC.^{93,94} It can appear in advanced stage of the disease⁹⁵ and particularly in *PLN* mutation carriers.^{96,97}

Epsilon waves are small amplitude deflections after the end of QRS but preceding the T wave. While epsilon waves are a major criterion for ARVD/C, we discourage their use when evaluating patients for ARVD/C. This reflects the fact that a recent study has shown very poor inter-reader reproducibility when panel experts were asked to identify Epsilon wave on ECG tracings of leads V1, V2, and V3.⁹⁸ Furthermore, this study revealed that epsilon waves do not impact the diagnosis of ARVD/C as they are only seen in patients with severe disease in whom the diagnosis is met on other structural and electrical criteria.^{11,98} In some difficult cases, Epsilon waves may be better observed with Fontaine lead system⁹⁹ or an insertable loop recorder.¹⁰⁰ Terminal activation delay, defined as duration from the nadir of S wave to the end of QRS ≥ 55 ms,¹⁰¹ is a minor criterion for depolarization abnormality. Although late potentials detected by signal-averaged electrocardiogram (SAECG) are also listed as a minor criterion for ARVD/C,⁸² we have found them to have poor sensitivity and specificity relative to other criteria and have therefore abandoned performing SAECGs when evaluating patients for possible ARVD/C.

Ambulatory Holter monitoring

Ambulatory Holter monitoring captures premature ventricular complex and sustained or non-sustained ventricular tachycardia, both of

which are important for diagnosis and follow-up in ARVD/C. The presence of >500 premature ventricular complex per 24 h is a minor TFC criterion⁸² while >1000 per 24 h is predictive of ventricular arrhythmia terminated by defibrillators.^{67,102} Ventricular tachycardia of left bundle branch pattern is consistent with ARVD/C diagnosis,⁸² and its presence is associated with arrhythmic risk.¹ Arrhythmogenic right ventricular dysplasia/cardiomyopathy patients can be followed by Holter annually to assess their risk of arrhythmia. Because electrical abnormalities on Holter monitoring may precede detectable structural changes in ARVD/C,¹⁰³ serial ambulatory Holter can be used for follow-up of family members to facilitate early diagnosis.

Echocardiography

Echocardiography is the first line imaging tool when ARVD/C is suspected. Right ventricular wall motion abnormalities, ventricular dilation, and reduced systolic function are included in the 2010 TFC.⁸² A RVOT long-axis diastolic dimension >30 mm occurred in 89% of probands and 14% of healthy controls.¹⁰⁴ Echocardiography has been used in clinical follow-up and showed marked variability in the rate of disease progression.^{105,106} However, more views than standard echocardiography are required to diagnose ARVD/C. Quantitative assessment of right ventricular function also requires high expertise but can lead to effective early detection of structural abnormalities¹⁰⁷ or even abnormal right ventricular deformation prior to structural abnormalities.¹⁰⁸

Cardiac magnetic resonance

Cardiac magnetic resonance is the preferred imaging modality for ARVD/C¹⁰⁹ in experienced centres in the absence of an implantable cardioverter-defibrillator (ICD). It provides comprehensive information on structural, functional, and tissue characterization of the ventricles. As in echocardiography, only wall motion abnormality, ventricular dilation, and systolic dysfunction are included in the 2010 TFC.⁸² Microaneurysm is not a criterion due to the concern of overuse of this term leading to false positive diagnoses. Although the presence of late gadolinium enhancement on CMR has been shown to be a diagnostic feature of ARVD/C and correlates with the myocardial fibro-fatty changes,¹¹⁰ this MRI parameter was not included in the 2010 Diagnostic Criteria. Despite this, we believe that it is of diagnostic value, especially those with the biventricular or left dominant forms. Myocardial fat and wall thinning are not diagnostic for ARVD/C either.¹¹¹ Nevertheless, tissue characterization on CMR deserves recognition and combining them to the 2010 TFC may improve diagnostic accuracy.¹¹² The location of wall motion abnormalities was not addressed in the 2010 TFC. Although the right ventricular apex is part of the initial report describing the triangle of dysplasia,² it is not typically affected in isolation. Instead, the basal inferior and anterior right ventricle, and the posterolateral left ventricle are commonly affected.¹¹³ Common normal variants mischaracterized as ARVD/C include right ventricular free wall tether, pectus excavatum, and isolated apicolateral bulge¹¹¹ (Figure 3). It is important to recognize that MR imaging is not the gold standard for diagnosis of ARVD/C but is only one of a number of diagnostic tests that should be considered when evaluating patients for suspected ARVD/C. In healthcare systems where CMR is not easily accessible, echocardiography in experienced hands using multiple views (with or without contrast medium or deformation imaging) can still very valuable.

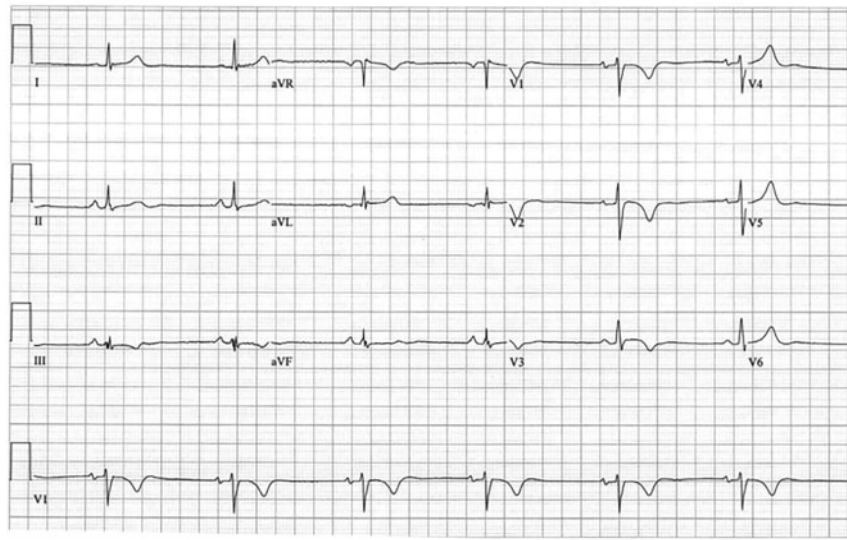


Figure 2 Typical 12-lead electrocardiogram from an ARVD/C patient. T wave inversion is present in lead V1–V3. ARVD/C, arrhythmogenic right ventricular dysplasia/cardiomyopathy.

Family history and genetic testing

Arrhythmogenic right ventricular dysplasia/cardiomyopathy is most commonly characterized by autosomal dominant inheritance with reduced penetrance. As a result, a definite diagnosis in first-degree family members is considered as a major criterion, even when no pathological mutation is detected in the family.⁸² According to a recent study, one third of first-degree relatives develop ARVD/C with siblings having the highest risk of disease.¹¹⁴

Genetic testing has been incorporated into the 2010 TFC. Genetic counselling and genetic testing is recommended for making the diagnosis in probands and as part of cascade screening of family members of probands with mutations.¹¹⁵ Mutations are detected in approximately 60% of index patients so the absence of mutations does not exclude the diagnosis.⁷⁸ Genetic testing is recommended to identify pathologic mutations in probands fulfilling phenotypic criteria and facilitate cascade screening of family members.¹⁸ The population prevalence of ARVD/C related mutations is unclear. A recent population-based study showed no phenotype in cases with definite loss of function desmosomal variants.¹¹⁶ Therefore, genetic testing is not recommended in individuals with only one minor 2010 TFC criterion and may be considered when one major or two minor criteria being met.¹¹⁷ Given the complexity in result interpretation and the rapid-evolving nature of genetics in ARVD/C, genetic counselling is strongly advised for patients and family members.¹¹⁸

Endomyocardial biopsy

The tissue characterization criteria in 2010 TFC focused on the severity of myocyte loss and specified the quantitative parameters of fibrosis.⁸² However, endomyocardial biopsy is invasive and its diagnostic sensitivity may be limited due to the patchy distribution of the disease. Although the right ventricular free wall is often affected, biopsy is usually taken from the septum for fear of perforation, which

further limits its sensitivity.⁴⁵ Immunohistochemical analysis of desmosomal protein localization is not specific for ARVD/C because similar disease patterns can also be seen in sarcoidosis and giant cell myocarditis.¹¹⁹ Today, endomyocardial biopsy is rarely performed. Its diagnostic value in ARVD/C is mainly for excluding other cardiomyopathies, myocarditis, and sarcoidosis.¹¹

Isoproterenol testing

Due to the high prevalence of catecholamine-facilitated ventricular tachycardia in ARVD/C,¹²⁰ ventricular arrhythmogenicity during isoproterenol testing has been proposed to assist diagnosis.¹²¹ In the article by Denis *et al.*,¹²¹ isoproterenol is infused continuously for 3 min at 45 $\mu\text{g}/\text{min}$. The test is considered positive if polymorphic premature ventricular contractions with at least 1 couplet or ventricular tachycardia of left bundle branch pattern but excluding RVOT origin is induced. Its sensitivity, specificity, positive, and negative predictive values to diagnose ARVD/C are 91.4%, 88.9%, 43.2%, and 99.1%, respectively. Although it is not included the 2010 TFC, its high sensitivity may help improve diagnosis in early disease stage. The high dose isoproterenol challenge is also being evaluated as a risk predictor in ARVD/C.

Differential diagnosis

The common differential diagnoses for ARVD/C are idiopathic ventricular tachycardia and sarcoidosis.¹¹ Other conditions to consider include dilated cardiomyopathy, pulmonary hypertension, and Uhl's disease.

Idiopathic ventricular tachycardia, either from RVOT or aortic sinus cusp, is usually associated with normal ECG and echocardiogram.¹²² A scoring system combining T-wave inversions in V1–V3, QRS duration in lead I ≥ 120 ms, QRS notching, and late precordial transition effectively distinguish idiopathic RVOT ventricular tachycardia from ARVD/C.¹²³ Ectopic QRS morphology (intrinsicoid deflection time > 80 ms, QS pattern in lead V1, and QRS axis $> 90^\circ$) has been reported recently to aid in differentiating idiopathic RVOT ventricular tachycardia from early

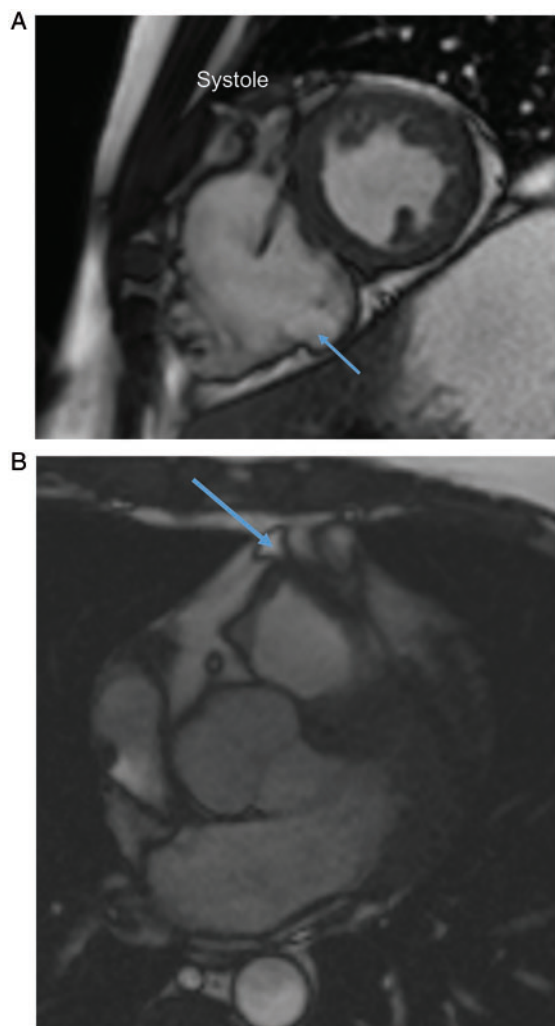


Figure 3 (A) Classic appearance of ARVD/C: systolic dyskinetic bulging in the inferior wall (arrow); (B) Tethering of the anterior wall (arrow) in a 55-year-old man without evidence of ARVD/C. ARVD/C, arrhythmogenic right ventricular dysplasia/cardiomyopathy.

ARVD/C.¹²⁴ Exhaustive work up is not needed when ECG and echocardiograph are normal and family history is negative for sudden death.

Cardiac sarcoidosis can overlap with ARVD/C. Older age of symptom onset, presence of cardiovascular comorbidities, non-familial pattern of disease, signs of conduction defect, significant left ventricular dysfunction, myocardial delayed enhancement of the septum, first degree or higher degrees of atrio-ventricular (AV) block, and mediastinal lymphadenopathy should raise the suspicion for cardiac sarcoidosis.¹²⁵ Cardiac position emission tomography can be very important for differential diagnosis.¹²⁶ Endomyocardial biopsy may be required to assist the diagnosis.

Biventricular ARVD/C with severe left side involvement may mimic dilated cardiomyopathy. Dilated right ventricle can also be seen in congenital heart disease such as Ebstein anomaly, Uhler's disease, anomalous venous return, pulmonary hypertension, or right ventricular infarction.¹¹

Management of arrhythmogenic right ventricular dysplasia/cardiomyopathy

The clinical management of ARVD/C patients consists of six aspects: (i) establishing an accurate diagnosis; (ii) risk stratification for sudden death; (iii) prevention of sustained ventricular arrhythmia; (iv) prevention of development of heart failure; (v) cardiac transplant; and (vi) screening and follow-up of family members. We will discuss each of this six-pronged approach here.

Establishing an accurate diagnosis

An accurate diagnosis is the premise of management. As above, lack of awareness of 2010 TFC and misinterpretation of CMR are the most common reasons for misdiagnosis.

Risk stratification for sudden death and decision for an implantable cardioverter-defibrillator

The prognosis of ARVD/C is predominantly related to ventricular arrhythmia which may lead to sudden death.⁷⁸ Its estimated overall mortality varies from 0.08% per year to 3.6% per year.^{82,127} Although not tested in randomized controlled trials, the efficacy of ICD therapy has been established by multiple observational studies.^{7,67,128–130} Between 40% and 78% of patients received appropriate ICD interventions after implantation. The survival benefit was estimated at 26%.¹²⁸ However, the benefit comes at the expense of device/lead-related complications (3.7% per year) and inappropriate ICD interventions (4.4% per year).^{1,102} Therefore, assessing sudden death risk is central in the disease management.

Commonly recognized predictors of life-threatening arrhythmia are summarized here. The strongest predictors are prior cardiac arrest from ventricular fibrillation and sustained ventricular tachycardia.⁴⁵ Other major risk factors include arrhythmogenic syncope, non-sustained ventricular tachycardia, and severe systolic dysfunctions of the right, left, or both ventricles.^{45,18} Premature ventricular complex count >1000 per day, T-wave inversion more than three leads, male sex, younger age at presentation, and proband status are minor risk factors.¹ Inducibility at electrophysiology study has been associated with ventricular arrhythmia treated by ICD from the Johns Hopkins and the Zurich experience^{67,102,130,131} but not in other studies.^{128,132} Atrial fibrillation may reflect electrical instability and has been associated with life-threatening arrhythmic events.⁶⁶ Risk of ventricular arrhythmia does not seem to significantly increase during pregnancy.¹³³ Unwillingness to restrict exercise has also been associated with higher risk of ventricular arrhythmia,^{17,62} The absence of risk factors confers a low risk of sudden death (<1% per year) and ICD is not indicated.¹

Based on the reported risk factors and estimated probability of life-threatening arrhythmic event, the International Task Force Consensus Statement on treatment of ARVD/C grouped patients in to high (>10% per year), intermediate (1–10% per year), or low risk categories (<1% per year)¹ (Figure 4). It is useful in the risk-benefit discussion with patients and family about whether the recommendation of an ICD is appropriate. Another critical variable is a specific

patient's preferences and values. Whereas some patients are unwilling to accept even a small risk of sudden death and consider placement of an ICD to be reassuring, other patients are adamantly against having an ICD implanted and are willing to accept a small risk of sudden death.

Single-chamber ICDs are recommended to minimize the risk of long-term lead-related complications especially in young patients. Although the number of inappropriate interventions may be decreased by a dual-chamber detection system, the additional lead predisposes to a higher risk of short and long term complications and should be only be employed in the setting of symptomatic bradycardia or AV block (which is virtually never seen in patients with ARVD/C).⁴⁵ Anti-tachycardia pacing is highly successful in terminating ventricular arrhythmia and should be programmed in all devices.¹³² The role of subcutaneous ICD is under investigation.

Prevention of sustained ventricular arrhythmias

Pharmacologic therapy is commonly utilized in the management of ARVD/C despite the lack of randomized clinical trials. Beta-blockers are recommended as the first line therapy for all definite ARVD/C patients.¹ This recommendation is an extrapolation of the beta-blockers' efficacy in sudden death prevention in heart failure.¹³⁴ It also relies on the observations that ventricular arrhythmia in ARVD/C is often effort-related and catecholamine-facilitated.¹²⁰

The use of anti-arrhythmic drugs rarely eliminates the risk of sudden death⁴⁵ and is mainly to reduce the arrhythmia burden.¹ If beta-blocker is ineffective, the conventional 'wisdom' is to try sotalol followed by amiodarone. However, evidence from cases series regarding the efficacy of sotalol and amiodarone have been conflicting.^{135,136} The addition of flecainide to beta-blockers may be effective according to a recent case series.¹³⁷ Overall, the use of anti-arrhythmic drugs is empirical. The field is awaiting well-designed clinical trials to guide the use of anti-arrhythmic drugs in ARVD/C management.

Catheter ablation is reserved for ARVD/C patients who fail pharmacologic therapies and continue to have frequent sustained or symptomatic non-sustained ventricular arrhythmias.¹ According to the 2015 Treatment Consensus, ARVD/C patients with incessant ventricular tachycardia (VT) or frequent ICD interventions on VT despite maximal pharmacological therapy should be referred for catheter ablation (Class I indication).¹ Despite a high short-term success rate, the major limitation of catheter ablation is the recurrence of sustained ventricular arrhythmias in 50-70% of patients' after 3–5 years of follow-up.^{138–141} Epicardial VT ablation or a combined endo-epi approach has been associated with improved short and long term efficacy with a 30% recurrence rate at 2 years of follow up.¹³⁸ New arrhythmogenic foci created by the progression of fibrofatty production may explain the not insignificant recurrence rate.¹⁴⁰ Nevertheless, catheter ablation is still an important palliative procedure to improve patients' quality life by reducing the arrhythmia burden. Bilateral sympathectomy may be considered for refractory ventricular arrhythmias.¹⁴²

Exercise restriction is recommended to all affected patients and desmosome mutation carriers.¹ This is because that exercise has been associated with development and severity of the ARVD/C

phenotype both in animal^{61,46} and human studies^{17,62,63,143} (Figure 5). Importantly, continuing to participate in competitive sports after diagnosis was associated with higher risk of ventricular tachyarrhythmia in definite and borderline ARVD/C probands.⁶² Desmosomal mutation carriers who remained in the top quartile of exercise duration after presentation had the higher risk of incident ventricular arrhythmia.¹⁷

Prevention of progression and development of heart failure

Few studies have examined structural progression in ARVD/C. It has been shown that structural dysfunction of the disease is progressive but with substantial interpatient variability.¹⁰⁵ As noted above, exercise restriction is believed to slow the disease progression. Because of the proven efficacy of angiotensin-converting enzyme inhibitors in heart failure, it has also been used for most patients with ARVD/C especially in the presence of structural changes.¹

Cardiac transplantation

Heart transplant is rarely needed in ARVD/C and is the last resort in case of either end-stage heart failure or debilitating lethal arrhythmia.⁸⁰ Patients requiring transplant often have disease onset at a younger age. Cardiac transplantation, when needed, is generally performed 10–20 years after initial presentation. Overall, the survival of patients with ARVD/C at 1, 5, and 10 years is 87%, 81%, and 77%, similar to non-ARVD/C recipients and better than ischaemic cardiomyopathy.¹⁴⁴

Screening approach to family members

After a proband is diagnosed with ARVD/C, there are three scenarios applicable to family members: (i) presence of a pathological mutation; (ii) absence of a pathological mutation, and (iii) presence of a variant of uncertain significance.⁴⁵ In the presence of a pathological mutation, mutation-specific 'cascade' genetic testing is recommended to identify mutation-carrying family members.¹⁸ Non-carriers are unlikely to develop the disease. For family members with disease-causing mutations, serial examination at one to three year intervals starting at the age of 10 years and exercise restriction are recommended.¹⁷ This serial screening should consist of an ECG, a Holter, and a CMR or echocardiogram. In the absence of a pathological mutation, ARVD/C is still considered hereditary and all family members are recommended to undergo diagnostic testing at 1–3 years intervals. When a variant of uncertain significance is identified, phenotyping of all at-risk relatives remains important and cascade genetic screening should not be performed to assist in clinical management (although it may assist in refinement of variant classification). Again, genetic counselling is strongly recommended in the management of ARVD/C.¹¹⁸

Direction for future research

Over the past three decades, much has been learned about diagnosis and treatment of ARVD/C. The complexity of the disease and advance in technology create tremendous opportunities to advance the care we deliver to these patients. Better delineation of the disease progression will deepen the understanding of its natural history and facilitate early diagnosis. As data interpretation catches up with the explosion of sequencing technology, we will have a better insight into its genetic aspect. Detailed and objective measurement of

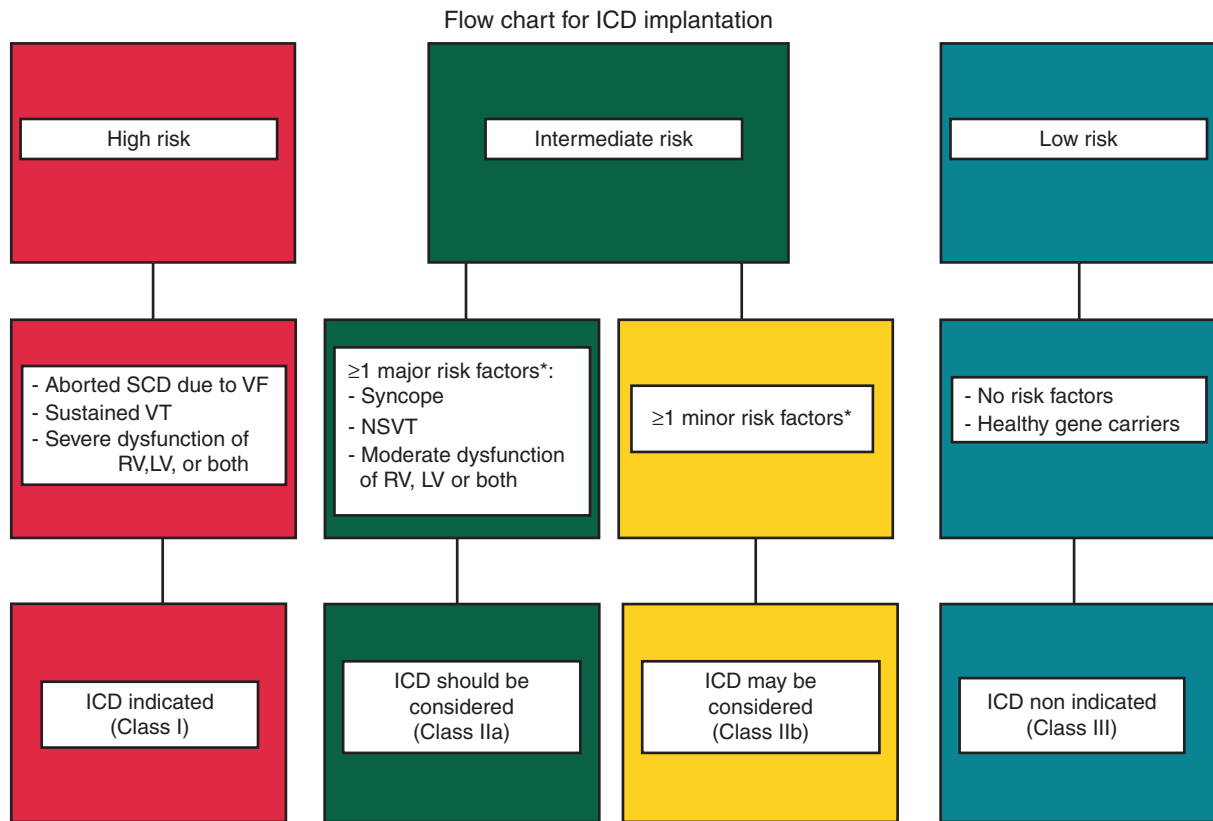


Figure 4 A flow chart of risk stratification and indications to ICD implantation in ARVD/C. From Corrado et al.¹ ARVD/C, arrhythmogenic right ventricular dysplasia/cardiomyopathy; ICD, implantable cardioverter-defibrillator; LV, left ventricle; RV, right ventricle; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia.

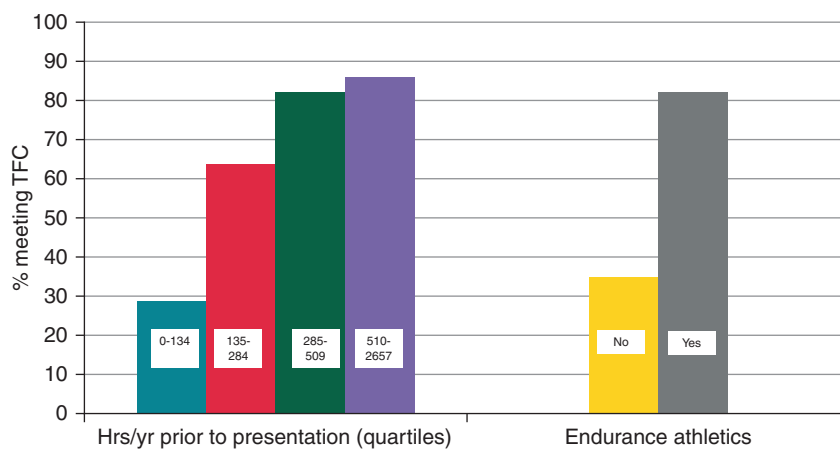


Figure 5 Likelihood of ARVD/C diagnosis is associated with exercise history. Likelihood of meeting diagnostic criteria at last follow-up is associated with increasing hours per year of exercise ($P < 0.001$) and participation in endurance athletics ($P < 0.001$). TFC = 2010 Task Force Criteria. From James et al.¹⁷ ARVD/C, arrhythmogenic right ventricular dysplasia/cardiomyopathy; TFC, Task Force Criteria. Reprinted with permission.

exercise exposure with prospective follow-up will make the personalized recommendation on exercise restriction possible. The refinement of risk stratification for sudden death will enable clinicians to implant an ICD in the right patients. Basic mechanistic research is needed in the search of curative therapy for the disease. At the end of the day, promising therapies will need to be tested in randomized controlled trials. Because ARVD/C is a rare disease, institutional and international collaboration will be required for these exciting endeavours.

Funding

This work was supported by the 2017 Clinical Research Award in Honor of Mark Josephson and Hein Wellens Scholarship from the Heart Rhythm Society (to W.W.). The authors wish to acknowledge funding from the Dr. Francis P. Chiamonte Private Foundation, the St. Jude Medical Foundation, and Boston Scientific Corp., and the Leducq foundation – RHYTHM Network (all to H.C.). The Johns Hopkins ARVD/C Program is supported by the Leyla Erkan Family Fund for ARVD Research, the Dr. Satish, Rupal, and Robin Shah ARVD Fund at Johns Hopkins, the Bogle Foundation, the Healing Hearts Foundation, the Campanella family, the Patrick J. Harrison Family, the Peter French Memorial Foundation, and the Wilmerding Endowments. H.C. receives research funding from Foundation Leducq (16 CVD 02).

Conflict of interest: none declared.

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