Arrhythmogenic Cardiomyopathy

Domenico Corrado, Cristina Basso, Daniel P. Judge

Abstract: Arrhythmogenic cardiomyopathy is an inherited heart muscle disorder, predisposing to sudden cardiac death, particularly in young patients and athletes. Pathological features include loss of myocytes and fibrofatty replacement of right ventricular myocardium; biventricular involvement is often observed. It is a cell-to-cell junction cardiomyopathy, typically caused by genetically determined abnormalities of cardiac desmosomes, which leads to detachment of myocytes and alteration of intracellular signal transduction. The diagnosis of arrhythmogenic cardiomyopathy does not rely on a single gold standard test but is achieved using a scoring system, which encompasses familial and genetic factors, ECG abnormalities, arrhythmias, and structural/functional ventricular alterations. The main goal of treatment is the prevention of sudden cardiac death. Implantable cardioverter defibrillator is the only proven lifesaving therapy; however, it is associated with significant morbidity because of device-related complications and inappropriate implantable cardioverter defibrillator interventions. Selection of patients who are the best candidates for implantable cardioverter defibrillator implantation is one of the most challenging issues in the clinical management. (Circ Res. 2017;121:784-802. DOI: 10.1161/CIRCRESAHA.117.309345.)

Key Words: arrhythmogenic right ventricular cardiomyopathy ■ arrhythmias, cardiac ■ cardiomyopathies ■ defibrillators, implantable ■ desmosomes

Arrhythmogenic cardiomyopathy (AC) is an inherited form of heart disease characterized pathologically by fibrofatty myocardial replacement and clinically by prominent ventricular arrhythmias and impairment of ventricular systolic function. Many credit the original description of this disorder to a article published in 1982 on arrhythmogenic right ventricular dysplasia although a previous report in French described this condition a few years earlier.1,2 The report in 1982 characterized 24 individuals with extensive substitution of the RV myocardium with fatty and fibrous tissue, who were referred to 2 hospitals in Paris. Subsequently, detailed pathologic features of the disease role in causing sudden death in athletes were reported by a prospective clinicopathologic study on the fatalities occurring in the young population of the Veneto region of Northeastern Italy.3 Initially, the histologic hallmark of disease, consisting of myocyte depletion with fibrofatty

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The online-only Data Supplement is available with this article at http://circres.ahajournals.org/lookup/suppl/doi:10.1161/CIRCRESAHA.117.309345/-/DC1.

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Circulation Research is available at http://circres.ahajournals.org

DOI: 10.1161/CIRCRESAHA.117.309345

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replacement, was thought to be the result of a congenital defect of myocardial development, and this perspective contributed to the early designation of dysplasia. As genetic and phenotypic characterization of the disease evolved, the term dysplasia was replaced by the designation of cardiomyopathy, which means a genetically determined heart muscle disorder and arrhythmogenic right ventricular dysplasia by arrhythmogenic right ventricular cardiomyopathy (ARVC).3,4 Many specialists have used the term ARVC/D or ARVD/C in an attempt to acknowledge the primary manifestation as a cardiomyopathy without losing the historic ties to the original description.5 Although the original disease phenotype was characterized by predominant RV involvement, with minor and late left ventricle (LV) disease, clinical variants characterized by early and greater LV involvement, which may parallel (ie, biventricular disease, clinical variants characterized by early and predominant RV involvement, with minor and late left ventricular dilatation with multiple free-wall aneurysms.4,19 Studies of SCD among athletes have shown that AC is responsible for this fatal presentation in 10% to 15% of cases.17,18 Most studies reported a higher incidence and greater severity of AC among men.19,20 This has been ascribed to the direct influence of sex hormones on the phenotypic expression of the disease or to the sex-related differences in the amount and intensity of exercise.21–23

**Pathology**

The hallmark lesion of AC is replacement of the ventricular myocardium by fibrofatty tissue.1,3,4 The condition should not be confused with Uhl disease, a congenital heart defect in which the RV myocardium fails to develop during embryonic life with the epicardium applied directly to endocardium in the absence of intervening fat.24 In AC, myocardial atrophy is a genetically determined process that occurs progressively with time, starts from the epicardium and extends toward the endocardium to become transmural, resulting into progressive wall thinning (Figure 1). As a consequence, the pathognomonic gross features of AC consist of single or multiple aneurysms, predominantly located in the so-called triangle of dysplasia, that is, inflow, apex, and outflow tract of the RV.1,3,4 However, up to 76% of the AC hearts studied at postmortem also disclosed involvement of the LV, which is usually limited to the subepicardial or midmural layers of the free wall.19 Hearts with end-stage disease leading to heart failure usually show huge biventricular chamber dilatation with multiple free-wall aneurysms.4,19

Genotype–phenotype correlation studies have demonstrated that the disease can have a phenotypic spectrum much wider than previously thought.9,10,25 The pathologic features range from grossly normal hearts at one end, in whom only a careful histopathologic investigation can reveal AC features in one or both ventricles, to hearts with massive biventricular disease involvement. Recently, an isolated, nonischemic LV fibrofatty scar, as seen either at postmortem examination or by post-contrast cardiac magnetic resonance (MR) sequences, has been reported to be a not uncommon myocardial substrate

### Nonstandard Abbreviations and Acronyms

| Abbreviation | Description |
|--------------|-------------|
| AADs         | antiarrhythmic drugs |
| AC           | arrhythmogenic cardiomyopathy |
| ARVC         | arrhythmogenic right ventricular cardiomyopathy |
| GSK3β        | glycogen synthase kinase 3β |
| ICD          | implantable defibrillator |
| ITF          | International Task Force |
| LV           | left ventricle |
| MR           | magnetic resonance |
| PPAR         | peroxisome proliferator–activated receptor |
| RV           | right ventricle |
| SCD          | sudden cardiac death |
| VF           | ventricular fibrillation |
| VT           | ventricular tachycardia |
| VUS          | variant of uncertain significance |

Northeastern Italy, where a systematic investigation of the causes of SCD in the young and a universal preparticipation screening strategy have identified affected individuals more commonly than in other countries. This led many to consider AC a Venetian disease; instead, it certainly occurs throughout the rest of Italy and Europe.9,10,11 Large cohorts sharing founder mutations are present in the Netherlands, and tracking of mutant haplotypes identified a distribution extending into North America.12 AC was first reported from South America as part of a syndrome involving woolly hair and palmoplantar keratoderma (Carvajal),13 and other forms of nonsyndromic AC also occur in Asia and Africa.14,15 Within the United States, most patients are white although some individuals with Asian and African ancestry also exist in well-characterized cohorts.16

The prevalence of AC among victims of SCD is relatively high, with AC ranking as one of the leading causes of sudden death in young people. A postmortem investigation of 60 young people (mean age, 22.3 years) with sudden death in the Veneto region of Italy for a 7-year period identified that 12 (20%) had AC on autopsy.3 In a US-based investigation of 100 people with AC, 31 (31%) were diagnosed postmortem.16 Studies of SCD among athletes have shown that AC is responsible for this fatal presentation in 10% to 15% of cases.17,18 Most studies reported a higher incidence and greater severity of AC among men.19,20 This has been ascribed to the direct influence of sex hormones on the phenotypic expression of the disease or to the sex-related differences in the amount and intensity of exercise.21–23

**Epidemiology**

The population frequency of AC has been estimated at 1:1000 to 5000. Investigators in one of these studies estimated its prevalence on the basis of the number of patients diagnosed with AC evaluated >7 years (n=80), normalizing this to the population served by a regional hospital (n=80 000), concluding the rate of 1:1000.7 Because the initial manifestation may be sudden cardiac death (SCD), undiagnosed patients probably make up an additional 30% in most populations.8 Yet, the prevailing opinion by most specialists in this area is that the prevalence is closer to 1:5000. The discordance may be related to frequent misdiagnoses. One report on the rate of misdiagnosis for AC identified that only 24 of 89 (27%) people referred to a tertiary center met the diagnostic criteria established at the time.9 AC is known to occur throughout the world. It has historically had a high prevalence in the Netherlands, where a systematic investigation of the causes of SCD in the young and a universal preparticipation screening strategy have identified affected individuals more commonly than in other countries. This led many to consider AC a Venetian disease; instead, it certainly occurs throughout the rest of Italy and Europe.9,10,11 Large cohorts sharing founder mutations are present in the Netherlands, and tracking of mutant haplotypes identified a distribution extending into North America.12 AC was first reported from South America as part of a syndrome involving woolly hair and palmoplantar keratoderma (Carvajal),13 and other forms of nonsyndromic AC also occur in Asia and Africa.14,15 Within the United States, most patients are white although some individuals with Asian and African ancestry also exist in well-characterized cohorts.16

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of life-threatening ventricular arrhythmias and SCD in young people and athletes. Of interest, this condition has been also linked in some cases to a genetically defective desmosome, suggesting that it may represent an additional phenotypic variant of AC manifesting as an exclusive and segmental involvement of the LV (segmental left-sided AC).26

Histological examination reveals islands of surviving myocytes, interspersed with fibrous and fatty tissue. Fatty infiltration of the RV is not a sufficient morphologic hallmark of AC, and replacement-type fibrosis and myocyte degenerative changes should always be identified. A certain amount of intramyocardial fat is present in the RV anterolateral and apical regions even in the normal heart, and myocardial fat increases with age and body size. Moreover, AC should be kept distinct from adipositas cordis. Myocyte degeneration and death are often associated with inflammatory infiltrates both in animal models and human patients. Myocardial inflammation has been reported in up to 75% of hearts at autopsy. In a transgenic animal model, myocyte necrosis was demonstrated to be the key initiator of myocardial injury, triggering progressive myocardial loss, followed by an inflammatory response. An apoptotic mechanism of myocyte death has also been proven. Rather than being a continuous, ongoing process, disease progression may occur through periodic acute bursts of an otherwise stable disease because to mimic myocarditis or myocardial infarction with normal coronary arteries. The detection of viral genomes led to consideration of an infective viral cause, but it is most likely that either viruses are innocent bystanders or myocardial cell degeneration may serve as a milieu favouring viral attachment.

The correct interpretation of autopsy findings is important because the postmortem diagnosis of AC in the proband enables cascade screening of living relatives with risk stratification for SCD and prophylactic treatment. An incorrect diagnosis of AC can lead to costly and extensive clinical evaluation of family members and expose them to the risk of overdiagnosis and possibly unnecessary implantation of a defibrillator. Therefore, the clinician should not hesitate to request a second opinion if any doubt exists that postmortem findings have not been properly interpreted.

**Cause and Pathogenesis**

**Genetics**

AC is a genetically heterogeneous disorder. A list of genes in which mutations are known to cause this condition is shown in the Table. Until 2000, little was known about the specific genes in which a pathogenic mutation would cause this unique form of cardiomyopathy. The preponderance of people with exclusively right-sided manifestations raised questions about genes with expression restricted to cells of second heart field origin. Linkage analysis identified several chromosomal loci associated with AC although this approach was limited because of low penetrance and small family sizes caused by the frequent occurrence of SCD. A hallmark discovery on the genetic basis of a related disorder, Naxos disease, eventually led to recognition of desmosome mutations causing AC. Naxos is an island in Greece where there is a cohort of people with palmoplantar keratoderma, distinctive woolly hair, and AC cosegregating in families in a recessive pattern. Homozygosity mapping and linkage analysis identified a haplotype on chromosome
17q21 among 21 affected individuals. Further analysis demonstrated that a homozygous frameshift mutation (c.2040_2041delGT) in JUP, encoding plakoglobin, causes Naxos disease.39 The next clue on the role of desmosome mutations in AC arose from South America, where Luis Carvajal-Huerta40 recognized a similar constellation of keratoderma, woolly hair, and AC with LV predominance. Because this is also a recessive disorder, genome-wide homozygosity mapping was applied to localize the genetic cause to chromosome 6p24. Further analysis determined that homozygous mutations in desmoplakin (DSP) cause this disorder.11 Two years later, the first report of a dominant DSP mutation causing nonsyndromic (ie, nonassociated with extracardiac features) AC was published.41 In a large family with AC, genome-wide linkage among affected individuals identified a common haplotype on chromosome 6p24. Based on the report of DSP mutations causing Carvajal syndrome and its close proximity to the locus, further testing identified mutation of a highly conserved serine (p.Ser299Arg) in desmoplakin that disrupts a site of phosphorylation and interferes with the binding of desmoplakin to plakoglobin.41

Because DSP and JUP are both components of the cardiac desmosome, Gerull et al 42 extended this research to another component of the cardiac desmosome. They investigated 120 probands with AC using the 1994 Task Force diagnostic criteria and identified heterozygous mutations in PKP2, encoding plakophilin-2, in 32 of 120 probands (27%). Remarkably, the majority of mutations (28/32 or 88%) caused premature truncation or frameshift alterations of the C terminus of the encoded protein.42 After recognition that PKP2 mutations are a common cause of AC, several additional candidate gene analyses facilitated reports of mutations in other components of the cardiac desmosome. Two groups reported several families with DSG2 mutations causing classic AC without abnormalities of the skin or hair.43,44 Next, DSC2 mutations were recognized to cause AC.45 Predictably, heterozygous mutations in JUP also cause nonsyndromic AC.46 Although the distribution of mutations among these 5 genes (PKP2, DSG2, DSP, DSC2, and JUP) varies among separate cohorts with AC, it is clear from multiple large studies that desmosome mutations are the most common cause of AC.

Although most nonsyndromic AC is inherited in an autosomal dominant pattern, recessive patterns also exist.22,47,48 Most large cohort studies of probands with AC report some carriers with multiple desmosomal gene mutations, either occurring in the same gene (compound heterozygosity) or in different genes (digenic heterozygosity). The prevalence of individuals with >1 desmosome mutation underlying their AC varies from 4% to 16%.22,49,50 Furthermore, those with >1 desmosome gene mutation are at higher risk of arrhythmia and SCD.22

Extending beyond the desmosome, the area composita is a mixed type of junctional structure composed of both desmosomal and adherens junctional proteins.51 Within the area composita, α-catenins are cytoplasmic molecules responsible for maintaining tissue morphogenesis by integrating in the cadherin–catenin complex and by interacting with the F-actin cytoskeleton.51 In heart tissue, α-T-catenin interacts directly with PKP2, linking adherens junctional and desmosomal proteins in the area composita.52 N-cadherin, which is an extracellular adherens junctional molecule, mediates calcium-dependent cell–cell adhesion and connects to the myocyte via α-catenin and β-catenin (plakoglobin).51 Mutations in CTNNA3, the gene encoding α-T-catenin, have been identified in 2 of 76 probands without a known desmosomal mutation.53 Recently, mutations in N-cadherin (CDH2) gene have also been found in 1 of 73 desmosomal gene–elusive AC probands54 and in 4 AC families (3,55 and with Alessandra Rampazzo, University of Padua, April 5, 2017, personal communication).

Pathogenic mutations in genes encoding components of the nuclear envelope can contribute to AC. LMNA encodes lamin isoforms A and C (lamin A/C), and mutations result in a remarkable array of phenotypes, including isolated AC. Emery–Dreifuss muscular dystrophy, limb-girdle muscular dystrophy type 1b, familial lipodystrophy, and Hutchinson–Gilford progeria.56 In addition to tachyarrhythmias, conduction delay is also common in patients with laminopathy. AC caused by LMNA mutations occasionally manifests as a predominantly RV cardiomyopathy but more often with biventricular dysfunction.57 Characterization of a large cohort in northern Canada facilitated discovery of a founder mutation in TMEM43, encoding another component of the nuclear envelope.58 After this first report, other mutations in TMEM43 have been reported in patients with AC.59

Desmin is a component of the intermediate filament, linking the nuclear membranes to the sarcolemma and Z-discs. DES mutations cause myofibrillar myopathy with prominent

### Table. Genes in Which Mutations Are Reported to Cause Arrhythmogenic Cardiomyopathy

| Gene   | Encoded Protein | Subcellular Localization | Chromosomal Locus |
|--------|-----------------|--------------------------|-------------------|
| JUP    | Junction plakoglobin | Desmosome | 17q21.2 |
| DSP    | Desmoplakin     | Desmosome | 6p24.3 |
| PKP2   | Plakophilin-2   | Desmosome | 12p11.21 |
| DSG2   | Desmoglein-2    | Desmosome | 18q12.1 |
| DSC2   | Desmocollin-2   | Desmosome | 18q12.1 |
| TMEM43 | Transmembrane protein 43 (luma) | Nuclear envelope | 3p25.1 |
| LMNA   | Lamin A/C       | Nuclear envelope | 1q22 |
| DES    | Desmin          | Intermediate filament | 2q35 |
| CTNNA3 | Alpha-T-catenin | Area composita | 10q21.3 |
| PLN    | Phospholamban   | SERCA        | 6q22.31 |
| TGFB3  | Transforming growth factor-3 | Growth factor | 14q24.3 |
| TTN    | Titin           | Sarcomere    | 2q31.2 |
| SCN5A  | Sodium voltage-gated channel alpha subunit 5 (NaV1.5) | Sodium channel | 3p22.2 |
| CDH2   | Cadherin C      | Area composita | 18q12.1 |
cardiac involvement. A cohort in the Netherlands with a founder mutation carries a missense mutation in this gene, p.Ser13Phe, affecting the N-terminal head domain. Because of the relatively high amount of desmin in the cardiac conduction system, DES mutations often manifest with conduction disease and heart block to a greater extent than skeletal myopathy. In another cohort of 91 AC probands, 2 (2%) had rare variants in DES, demonstrating that the contribution of desmin to AC is relatively low.

Phospholamban normally inhibits the sarcoplasmic reticulum calcium transport ATPase, which is a pump that transports calcium ions to regulate cardiac contractions. PLN mutations cause dysregulated calcium flux, predisposing to prominent arrhythmia and ventricular dysfunction. Despite the small size of PLN, mutations in this gene are relatively common in European cohorts with AC. A founder mutation of PLN, p.Arg14del, is present in 10% to 15% of probands with AC in the Netherlands.

SCN5A encodes Na\textsubscript{v}1.5, the pore-forming subunit of the voltage-gated cardiac sodium channel. Mutations in SCN5A cause Brugada syndrome, familial dilated cardiomyopathy, and atrial fibrillation. PKP2 coprecipitates with Na\textsubscript{v}1.5, and loss of PKP2 expression alters the amplitude and kinetics of the sodium current (I\textsubscript{Na}). Recently, a large multicenter collaborative study identified that ≈2% of probands with AC have a pathogenic SCN5A mutation, expanding the spectrum of phenotypes associated with mutations in this gene.

One of the earliest linkage analyses identified a locus at chromosome 14q24.3 that cosegregated with AC. The initial analysis of genes in or near this locus did not identify any pathogenic mutations. Despite this negative result, investigators continued to examine this locus, later identifying variants in both the 5' and 3' untranslated portions of TGFB3, encoding transforming growth factor β-3. Subsequent studies have also identified TGFB3 mutations in the context of aortic aneurysms and features of Loeys-Dietz syndrome. Among patients with AC and either a personal history or family history of aortic aneurysm, bifid uvula, cleft palate, or hypertelorism, TGFB3 mutations should be considered.

Pathogenesis

Full understanding of the pathogenesis of this uncommon form of cardiomyopathy is currently lacking, but several contributing factors are now well recognized (Figure 2A). Discovery that desmosome mutations cause AC turned attention toward this subcellular structure, which mediates intercellular connections. The simplest explanation for desmosome mutations causing cardiomyopathy relies on loss of adhesion between cardiac myocytes, which predisposes them to detachment and death with replacement by fibrofatty tissue. Exercise exacerbates this adhesion defect, with greater consequence for the thinner walled RV as compared with the LV.

Clinicopathologic studies demonstrated that AC is a leading cause of sport-related SCD. In addition, experimental animal studies highlighted the potential role of exercise contributing to the pathogenesis of AC, with multiple murine models demonstrating that exercise exacerbates the phenotype. The role of exercise as a disease modifier was confirmed by clinical studies on desmosomal gene mutations carriers. Individuals engaged in endurance sports became symptomatic at an earlier age, had an increased likelihood of developing an overt phenotype, and showed worse survival free from ventricular arrhythmia and heart failure. Other than specialized structures that provide mechanical cell attachment, desmosomes are important mediators of intra- and intercellular signal transduction pathways. Alteration of the desmosome because of AC causes redistribution of plakoglobin from the cell surface to the nucleus. Plakoglobin, also known as γ-catenin, competes with β-catenin for nuclear translocation and activation of canonical Wnt signaling. Suppression of canonical Wnt signaling because of desmosome perturbation was first demonstrated in a myocyte cell culture system using short interfering RNA to reduce the content of desmoplakin. This led to reduced activity of canonical Wnt transcription factors. Although cardiac-restricted deletion of Dsp in mice has a high rate of embryonic lethality in homozygosity, heterozygous Dsp-deficient mice recapitulate human AC, with fibrosis and adiposity in the ventricular myocardium and increased nuclear plakoglobin, associated with markers of reduced Wnt signaling.

Before 2009, the origin of adipocytes in hearts with AC was unknown. Clever experiments using lineage-tracing mice helped to clarify the origin of this uncommon histological finding. In these studies, adipocytes in mice with AC seem to originate from second heart field cardiac progenitor cells (Figure 2B), and nuclear accumulation of plakoglobin suppresses canonical Wnt signaling, increasing adipogenic factors (noncanonical Wnt5b and bone morphogenetic protein-7) and reducing inhibitors of adipogenesis (connective tissue growth factor). Previous studies in skeletal muscle had identified a subset of progenitor cells characterized by the presence of a cell-surface marker, platelet-derived growth factor receptor-α. These cells differentiate into myogenic stem cells, fibroblasts, or adipocytes, depending on the context and pattern of injury to skeletal muscle although the presence or role of similar cells were previously unknown in the heart. Lombardi et al isolated myocyte-depleted cardiac cells and sorted them by flow cytometry to select for the presence of platelet-derived growth factor receptor-α, but notably without other cell lineages markers. Further analysis showed that these cells have bimodal potential for differentiation into fibrogenic or adipogenic pathways and were accordingly designated fibroadipocyte progenitor cells. Supporting their role in the pathogenesis of AC, cardiac fibroadipocyte progenitors express desmosome genes and their differentiation into adipocytes is enhanced by suppression of canonical Wnt signaling. This discovery helped to expand the cellular spectrum implicated in the pathogenesis of AC from one that was mostly focused on cardiac myocytes to one more broadly implicating fibroblasts and their precursors. Investigation of PKP2 deficiency in a cardiac cell line also identified downregulation of micro-RNA-184 (miR-184) as an important contributor to adipogenesis in the heart.

Validating the role of canonical Wnt in the pathogenesis of AC, therapies designed to increase Wnt signaling improve features of AC. A chemical screen with zebrafish expressing the Naxos mutation in plakoglobin identified SB216763, an inhibitor of glycosgen synthase kinase 3β (GSK3β), as a drug...
that improves features of AC. GSK3β is a negative regulator of canonical Wnt signaling, and inhibition of GSK3β activates this pathway. In this model, untreated mutant fish had pathological redistribution of plakoglobin, connexin-43, and Na_1.5 without reduction in their overall cellular content, implicating defective protein trafficking in the intercalated discs in response to mutant plakoglobin. Subsequent treatment with SB216763 using 2 other murine models of AC also showed improvements in cardiac histopathology, arrhythmia, function, and survival. Highlighting a more central role for GSK3β, desmosome mutations lead to reduced cytoplasmic localization of GSK3β and redistribution to the intercalated discs, both in murine models and in people with AC but not in other forms of cardiomyopathy. This suggests a more central role for GSK3β in the pathogenesis of AC.

Focusing on proteins that localize to the intercalated disc, subsequent investigation pursued the hypothesis that desmosome mutations could alter the Hippo pathway, an important regulator of organ size whose name arises from recognition that loss-of-function mutations in its components can lead to hippopotamus-like overgrowth. Hippo plays an important role in cell proliferation, differentiation, and apoptosis. Neurofibromin-2 (also known as Merlin) localizes to the intercalated disc among other places, and this multifunctional protein regulates cell–cell and cell–matrix adhesions, acting upstream in the Hippo pathway. In the context of AC, investigators postulated that mutations altering the intercalated disc would alter Hippo signaling by affecting neurofibromin-2 and thereby contribute to the development of fibroadiposis in the heart. Using a combination of human heart tissue from patients with AC, cultured myocytes with Pkp2 knockdown, and mice with mutations in Jup and Dsp, they demonstrated multiple markers of increased Hippo pathway activation. Activation of the Hippo pathway and inactivation of YAP (Yes-associated protein), which is an effector of the Hippo pathway and binds to both β-catenin and γ-catenin, have been implicated in the enhancement of adipogenesis. Activation of the Hippo pathway also suppresses canonical Wnt signaling, further confirming its role in the pathogenesis of AC.

As with many other genetic heart diseases, investigation of induced pluripotent stem cells differentiated to form cardiac myocytes has been applied to AC. Because people with AC typically have normal hearts at birth and for many years thereafter induced pluripotent stem cells differentiated to form cardiac myocyte studies of AC required induction of a more adult-like environment to evoke its pathological...
features. Although neonatal cardiac myocytes typically rely more on glucose for metabolism, adult cardiac myocytes rely on oxidation of fatty acids as their primary metabolic source.\(^\text{93}\) Induction of fatty acid oxidation in induced pluripotent stem cells differentiated to form cardiac myocytes using compounds that activate PPAR\(\gamma\) (peroxisome proliferator–activated receptor–\(\gamma\)) and PPAR\(\alpha\) recapitulated several cellular features of AC, including exaggerated lipogenesis and apoptosis in cells with PKP2 mutations compared with controls.\(^\text{92}\)

Another line of investigation about the pathogenesis of AC is focused on interactions between the desmosome and the sodium channel complex.\(^\text{68,69,95}\) High-resolution, nanoscale imaging demonstrates aggregation of voltage-gated sodium channels with cell adhesion molecules, such as N-cadherin.\(^\text{96}\) This helps to explain some of the distinct overlap between phenotypes such as Brugada syndrome and AC.\(^\text{95}\) Additionally, mutations in desmosome genes lead to reduced sodium current and may associate with a Brugada syndrome phenotype.\(^\text{97}\) and mutations in genes encoding elements of the sodium channel complex may cause AC.\(^\text{70}\) These findings are consistent with the observation that reduction in the sodium current density and slowing of conduction in the heart may precede structural heart disease caused by desmosome mutations.\(^\text{98}\)

One unanswered question about the mechanisms whereby desmosome mutations cause AC arises from disparate reports for haploinsufficiency versus dominant negative interference induced by specific mutations. Several reports have shown that knockout of the cardiac desmosome genes causes embryonic lethality, whereas heterozygous knockout mice do not have a phenotype unless provoked by exercise.\(^\text{99,100}\) Multiple transgenic strains of mice overexpressing desmosome mutations have been reported with features of AC.\(^\text{71}\) Modulating the role of nonsense-mediated RNA decay in mice with Jup mutations, investigators generated an allelic series of mice with Jup knock-in mutations.\(^\text{101}\) Homozygotes with a 2 bp deletions and nonsense mutation amenable to nonsense-mediated RNA decay had severely reduced Jup mRNA and neonatal lethality. However, the same mutation with genetic engineering designed to evade nonsense-mediated RNA decay results in normal mRNA levels encoding a truncated form of plakoglobin and a surprising lack of cardiac pathology.\(^\text{101}\) Further support for haploinsufficiency for components of the cardiac desmosome arises from the prevalence of heterozygous PKP2 truncations among people with AC.\(^\text{42}\) Unfortunately, these findings cannot be applied to all desmosome mutations because some unequivocally missense mutations alter known functional domains in cardiac desmosome proteins, such as the R-X-K-R domain of desmoglein-2, where cleavage by an enzyme known as furin is required and where heterozygous mutations reproducibly cause AC despite normal levels of mRNA.\(^\text{43}\) These findings indicate complexity in the pathogenesis of AC because of desmosome mutations.

**Genetic Testing**

Genetic testing has evolved considerably over the past decade although many shortcomings persist. Technological improvements have increased the availability and lowered the costs for genetic analysis in patients with all forms of cardiomyopathy. These improvements have broadened the availability of genetic testing in clinical practice because the cost of DNA sequence analysis of a large panel of genes related to cardiomyopathy may be even lower than the cost of obtaining and interpreting an echocardiogram.\(^\text{102}\) The availability of molecular testing for mutation screening of desmosomal and nondesmosomal genes offers the possibility to identify genetically affected individuals in the clinical setting. This technology frequently identifies novel DNA variants of uncertain significance, and for most genes associated with AC, quantitative functional analysis of these variants is not possible. Sometimes next-generation sequencing does not provide complete coverage of relevant genes, and unless a clinical method specifically includes its assessment, next-generation sequencing may not identify some deletions, duplications, insertions, or rearrangements. In addition, the normal human reference sequence was based on limited information until recently. Large public databases can now easily be searched to determine the prevalence of rare DNA variants. However, a recent report emphasized the potential for genetic misdiagnoses among patients who were not white undergoing genetic testing for hypertrophic cardiomyopathy.\(^\text{103}\)

Like all forms of familial cardiomyopathy, AC is genetically heterogeneous. Yet, in contrast with other forms of cardiomyopathy, the presence of a gene mutation is a criterion to make the diagnosis.\(^\text{3}\) However, population studies have shown that variation in genes related to AC is common, and major mutations are sometimes present in controls.\(^\text{104}\) With these issues in mind, it is important that the diagnosis of AC is based primarily on the structural, histopathologic, and arrhythmic manifestations of the disease in the proband within a family. Current guidelines recommend that the initial genetic testing within a family should only be applied to probands with an unequivocal phenotype.\(^\text{105}\)

Within a family in which a proband has been diagnosed with AC, there are 3 scenarios applicable to family members: the presence of a clear pathological mutation, absence of a clear pathological mutation, and the presence of a DNA variant of uncertain significance (VUS). If a clear mutation is recognized in an unequivocally affected proband, then cascade screening within the family helps to identify others at highest risk for developing AC. Despite the absence of a clear mutation in a proband, AC is still considered a genetic form of cardiomyopathy, and all first-degree relatives should undergo phenotypic screening. Genetic testing increasingly identifies novel sequence variants without clear evidence of pathogenicity. The strength of evidence for pathogenicity in a VUS can range from weak to strong, but any uncertainty still prohibits their use in the evaluation of unaffected family members. Targeted testing for a VUS in other affected family members can exclude its primary role when a lack of cosegregation is recognized. Increasing levels of cosegregation of AC and a VUS within a family can help to build support for
pathogenicity. Additional standards and guidelines for consideration with VUSs are available.106

Diagnosis

Clinical Manifestations
The phenotypic expression of AC varies considerably, ranging from the clinical profiles of asymptomatic family members with concealed structural abnormalities and no arrhythmias to symptomatic patients experiencing arrhythmic cardiac arrest or undergoing cardiac transplantation because of refractory heart failure.19,107–111 The most common clinical presentation consists of ventricular arrhythmias and related symptoms/events, which include palpitations, syncopal episodes (mostly occurring during physical exercise), and cardiac arrest. SCD may occur unexpectedly in previously asymptomatic individuals, mostly young people and competitive athletes, with a previously undiagnosed (and unsuspected) AC.3,73–75 The clinical presentation of AC may occasionally simulate acute myocarditis, characterized by chest pain, transient ST-segment and T-wave changes, and increased muscle enzyme levels, with or without ventricular arrhythmias.31 The diagnosis of biventricular or predominant left AC may be missed at onset of symptoms in some patients who present years later with heart failure, with or without ventricular arrhythmias, and are incorrectly diagnosed as having idiopathic dilated cardiomyopathy.19,20

The prognosis of AC is related to either ventricular electric instability, which may lead to arrhythmic SCD, or progression of ventricular muscle disease resulting in RV or biventricular systolic dysfunction. The overall mortality rate varies among different studies, ranging from 0.08% per year during a mean follow-up of 8.5 years in the series by Nava et al112 to 3.6% per year during a mean follow-up of 4.6 years in the series by Lemola et al.113 This high variability depends on the different populations considered in these studies, and it reflects the wide spectrum of AC clinical presentations and the presence of subgroups with variable penetrance and SCD risk. The adverse prognosis of AC patients was initially overestimated by early reports of patients with severe clinical manifestations. By contrast, subsequent studies of a broader AC patient population, including asymptomatic family members and genetically affected individuals with no phenotypic manifestations, have reported significantly lower SCD rates.109,110

The following stages in the natural history of classical right-sided AC can be considered:107 (1) The initial phase is named concealed because there are no or subtle RV structural changes, with or without minor ventricular arrhythmias. Nevertheless, SCD may occur at this early stage as the first manifestation of the disease in previously asymptomatic young individuals. (2) The second phase of clinically overt disease is characterized by the occurrence of RV arrhythmias in association with manifest RV functional and structural abnormalities, which are detectable by current imaging tests. Patients may experience arrhythmic symptoms such as palpitations, syncope, or cardiac arrest. (3) The third phase is caused by the progression of RV muscle disease leading to RV failure because of global RV contractile impairment, with a relatively preserved LV function. (4) The end stage of biventricular pump failure is characterized by parallel significant LV involvement with systolic dysfunction. At this stage, AC may mimic dilated cardiomyopathy of other causes with its related complications such as atrial fibrillation and thromboembolic events.

SCD in AC is caused by an arrhythmic cardiac arrest because of sustained ventricular tachycardia (VT) or ventricular fibrillation (VF). Patients with clinically overt disease may experience reentrant sustained VT in relation to a fibrofatty ventricular scar.114,115 Ventricular arrhythmias are worsened by adrenergic stimulation and neuroautonomic imbalance occurring during or immediately after exercise.74,116 Abrupt ventricular fibrillation may be precipitated by acute ventricular electric instability during an active phase of disease progression (hot phase), in relation to acute myocyte death with reactive myocardial inflammation. More recently, insights from experimental animal models led to postulation that gap junction remodeling, and molecular cross talk between desmosomes and sodium channels act primarily as an electric substrate for lethal arrhythmias, which can take place even before the development of fibrofatty myocardial replacement (prehistologic phase of the disease).58,69,95

Diagnostic Criteria
Because there is not a single gold standard diagnostic tool, the best strategy consists in reaching clinical diagnosis by combining multiple sources of clinical information, such as genetic, electrocardiographic, arrhythmic, morphofunctional, and histopathologic findings. In 1994, a scoring system for clinical diagnosis of ARVC was proposed by an International Task Force (ITF). Based on their diagnostic accuracy, criteria were classified as major and minor, and the diagnosis of ARVC was fulfilled in the presence of 2 major criteria, 1 major plus 2 minor, or 4 minor criteria from different categories.117 Although the ITF criteria have been useful for differentiating between ARVC and dilated cardiomyopathy or idiopathic right ventricular outflow tract tachycardia, they have shown a lack of sensitivity for identification of early/minor phenotypes, particularly in the setting of familial ARVC. In 2010, a revision of diagnostic guidelines was proposed with the aim to improve specificity of the diagnosis in probands and first-degree relatives.3 In this regard, molecular genetic information has been added to family history criteria and the presence of a disease-causing gene mutation has become a major criterion for the diagnosis of AC (Table I in the Online Data Supplement).

Repolarization and Depolarization Abnormalities
Twelve-lead ECG is a valuable diagnostic test in AC because it records repolarization and depolarization abnormalities in the majority of probands with a definitive diagnosis of AC (Figure 3).118 Negative T waves in the anterior precordial leads (V1 through V4) are the most common finding.3,4,10,11,118 The reported prevalence of these repolarization abnormalities ranges from 19% to 94% and is higher among probands with overt clinical manifestation than among relatives showing early/minor phenotypic expression.108–110 Negative T waves may extend to lateral precordial leads (V5 and V6), suggesting
a diffuse fibrofatty myocardial replacement with severe RV dilatation and LV involvement.\textsuperscript{119} The ECG of predominant left AC is characterized by isolated T-wave inversion in the lateral precordial leads.\textsuperscript{120}

Depolarization abnormalities include incomplete (rarely complete) right bundle branch block, prolongation of right precordial QRS duration with a delayed S-wave upstroke (terminal activation delay >55 ms), QRS fragmentation, and post-excitation epsilon waves (ie, small amplitude potentials occurring at the end of QRS complex/beginning of the ST segment).\textsuperscript{121,122} These ECG changes reflect areas of slow intraventricular conduction, in which the underlying substrate consists of regions of surviving myocardium interspersed with fatty and fibrous tissue. These can cause fragmentation of the electric activation of the ventricular myocardium and predispose to reentrant ventricular arrhythmias.\textsuperscript{114,115} Epsilon waves are recorded in patients with advanced disease, who fulfill other major diagnostic criteria for AC. A large interobserver variability in the ECG diagnosis of epsilon waves has been reported, suggesting that this ECG pattern should be evaluated with caution, especially in patients without other diagnostic criteria.\textsuperscript{122}

Activation delay can also be detected as late potentials in the terminal portion of the QRS complex by signal-averaged ECG techniques (Figure 3C).\textsuperscript{5}

**Ventricular Arrhythmias**

The spectrum of ventricular arrhythmias in AC ranges from isolated premature ventricular beats to sustained VT or VF leading to cardiac arrest.\textsuperscript{3,4,19,108–111} The arrhythmia severity varies from patient to patient and during the course of the disease. According to revised ITF diagnostic criteria, the morphology of VT, either sustained or nonsustained, has a different diagnostic impact.\textsuperscript{5} Ventricular tachycardia with a left bundle branch block and inferior axis pattern is considered a minor diagnostic criterion because of its low specificity, which may lead to misdiagnosis of AC in patients with idiopathic right ventricular outflow tract-VT. Moreover, VT with a left bundle branch block and superior or indeterminate axis pattern is more specifically observed in patients with AC and, thus, are classified as major diagnostic criteria (Figure 3E). It is noteworthy that in left-sided variants of AC, ventricular arrhythmias show a right bundle branch block morphology, which denotes their origin from the LV.\textsuperscript{120}

Although the rate of sustained ventricular tachycardia may be rapid, it is hemodynamically well tolerated in patients with AC who usually have a normal (or slightly reduced) systolic LV function.\textsuperscript{123}

Sustained monomorphic ventricular tachycardia can be induced during electrophysiologic study by programmed ventricular stimulation. This test may provide valuable
information about the inducibility of ≥1 VTs with different rates and morphologies, which may be useful in differentiating AC from idiopathic right ventricular outflow tract-VT, which is usually benign and nonfamilial. In contrast with AC-related VT, idiopathic right ventricular outflow tract-VT is characterized by a single morphology (left bundle branch block/inferior axis) and is not inducible by programmed ventricular stimulation.

Abrupt VF may lead to SCD any time during the disease course. However, patients experiencing VF/SCD are often significantly younger (median age, 23 years) than those presenting with sustained monomorphic VT (median age, 36 years). This finding is consistent with the concept that ventricular fibrillation predominantly affects young patients with a progressive and pathobiologically active myocardial disease, characterized by inflammatory-mediated acute cell death. On the contrary, hemodynamically well-tolerated monomorphic ventricular tachycardia is caused by a reentry mechanism around a stable myocardial scar as the result of a repair process that occurs in a later stage of the disease.

Global or Regional Dysfunction/Structural Alterations
Relevant structural and functional abnormalities include global RV dilatation, with or without a decreased ejection fraction, and regional wall motion abnormalities (Figure 4). RV angiography has been long regarded as the gold standard imaging test for the diagnosis. Angiographic evidence of systolic akinesia/dyskinesia and diastolic bulging localized in infundibular, apical, and subtricuspid regions provides a diagnostic specificity of >90%. Echocardiography is noninvasive and represents a first-line imaging approach to evaluate patients with suspected AC or to screen family members. Echocardiography also is useful for serial examinations during the clinical follow-up of affected patients.

In recent years, contrast-enhanced cardiac MR imaging has become in the recent years an integral part of diagnostic evaluation of AC. Besides determining the presence of morphofunctional ventricular abnormalities, cardiac MR allows myocardial tissue characterization by late gadolinium enhancement, which provides information of the presence, morphology, and wall distribution of myocardial fibrofatty scar (Figure 4B). Of great importance is the potential diagnostic value of late gadolinium enhancement technique for early diagnosis of structural abnormalities of AC. This imaging modality provides greater sensitivity to detect early structural myocardial lesion, which is often manifest as nontransmural fibrosis of a LV segment, otherwise undetectable by echocardiography/angiography because it is not large enough to induce a systolic wall motion abnormality.

Cardiac MR may increase the risk of AC misdiagnosis because of the difficult (and operator dependent) interpretation of RV wall motion abnormalities, which represent major criteria for the diagnosis. This translates into large interobserver variability and low specificity and makes misinterpretation of cardiac MR findings the most frequent cause of overdiagnosis. A corollary is that physicians should use extreme caution in reaching the diagnosis (or raising a suspicion of AC) whether structural tissue abnormalities or other diagnostic criteria are lacking.

Three-dimensional electroanatomic voltage mapping by CARTO system (Biosense, Diamond Bar, CA) may be of significant added value for the diagnosis of AC because it has the potential to identify and quantify RV regions of scar with low-amplitude voltage.
electric signals, which typically show fractionation, double potentials, or conduction delay. However, it is not recommended as a routine diagnostic tool because it is invasive, expensive, and highly operator dependent with a significant risk of inaccurate interpretation of low-voltage recordings in areas of normal myocardium because of suboptimal catheter contact.

**Histopathology**

Transvenous endomyocardial biopsy (EMB) has been part of the diagnostic evaluation of AC since 1994. This technique offers the potential for in vivo histologic tissue characterization with demonstration of the hallmark disease lesion, that is, loss of RV myocytes with fibrofatty replacement (Figure 4D), which is a major criterion for the clinical diagnosis of AC.

The sensitivity of EMB for AC is low if the myocardial samples are taken from the septum, which is a region uncommonly involved by the disease. In patients with AC, samples should be obtained from the RV free wall because the fibrofatty replacement is usually transmural and thus detectable from the endocardial approach. To improve the diagnostic sensitivity and avoid the risk of wall perforation, an EMB procedure guided either by voltage mapping or by MRI has been suggested. There is some difficulty in differentiating AC from other causes of fatty infiltration of the RV myocardium or the normal amount of subepicardial adipose tissue, which has been reported in the human heart. In this regard, the revised ITF criteria introduced quantitative parameters for histopathologic evaluation of EMB samples, focusing on the severity of myocyte loss and fibrous repair rather than on fatty infiltration of myocardium.

EMB cannot be routinely recommended for diagnosis of AC and should be reserved for selected patients particularly probands with a sporadic form of AC, in whom the final diagnosis depends on histologic exclusion of phenocopies such as dilated cardiomyopathy, myocarditis, or sarcoidosis.

An immunohistochemical analytical test of EMB samples for the diagnosis of AC has been developed, with the aim of identifying changes in the distribution of desmosomal proteins. Initial data with the use of the test showed that a markedly reduced signal for JUP at intercalated discs was an accurate disease biomarker. However, more recent data indicate that a reduced desmosomal protein signal is not specific for AC because it is also found in patients with sarcoidosis and giant cell myocarditis. In 1 small study, abnormal redistribution of GSK3β seemed to have greater specificity for the diagnosis of AC, but confirmatory studies are needed.

**Therapy**

**Risk Stratification**

Risk stratification depends largely on evaluation of the severity of AC phenotypic expression in terms of severity of arrhythmic manifestations and amount of fibrofatty myocardial replacement as evaluated by electrocardiographic tests and imaging. Follow-up studies have identified several risk factors, but the assessment of the relative weight of each prognostic marker is difficult because of the small sample sizes and the heterogeneity of variables tested in each study.

There is general agreement that a history of cardiac arrest because of ventricular fibrillation or sustained VT confers the highest risk of SCD. The prognostic role of unexplained syncope (ie, non-neuromediated) and nonsustained VT is controversial because it has been associated with an increased arrhythmic risk in some but not in all studies. Moderate to severe systolic dysfunction of the RV, LV, or both has been consistently found to be independent predictors of poor outcome in prospective studies. Among ECG parameters, greater extent of T-wave inversion across the 12 leads has been associated with unfavorable arrhythmic prognosis during follow-up. Different studies provided conflicting results about the prognostic role of VT/VF inducibility by programmed ventricular stimulation. Two large multicenter studies on patients who received an implantable defibrillator (ICD) for either primary or secondary prevention showed that the incidence of life-saving interventions on fast VT/VF did not significantly differ between patients who were and were not inducible at pre-implant programmed ventricular stimulation.

The North American Multidisciplinary study confirmed that inducibility of VT or VF did not predict appropriate interventions on fast VT/VF during follow-up of ICD carriers with AC. On the contrary, studies from Johns Hopkins reported that inducibility was the most significant independent predictor of appropriate ICD interventions for any VT but not for shocks on fast VT or VF. Likewise, the Swiss study by Saguner et al showed that inducibility of VT was an independent predictor of a composite end point including cardiac death, heart transplantation, unstable VT/VF, and syncope.

Male sex and multiple gene mutations are significant genetic factors that impact the prognosis of AC. Compound or digenic heterozygosity is an independent predictor of more severe lifetime arrhythmic outcome.

**Clinical Management**

The most important objective of clinical treatment of AC patients is prevention of SCD. Current therapeutic options include lifestyle changes, β-blockers, antiarrhythmic drugs (AADs), catheter ablation, ICD, and heart transplantation. Recently, a task force of experts from both Europe and the United States produced a consensus document for treatment of AC. This ITF document provides a summary of evidence and a set of recommendations aimed to prevent SCD in patients at risk and avoid overtreatment in asymptomatic patients or healthy gene carriers.

**Lifestyle Changes and β-Blockers**

Physical exercise is one of the most important factors, which promotes the phenotypic expression of the disease, and is a principal factor, which triggers life-threatening ventricular arrhythmias in AC. Endurance athletics are sports with a high dynamic demand (>70% maximum O2 consumption), as defined by the 36th Bethesda Conference Classification of Sports (Task Force 8). β-blocker therapy should be considered as an additional antiadrenergic treatment in patients with AC because of its ability to lower the risk of exercise-induced ventricular arrhythmias and to hinder myocardial disease progression by
lowering the ventricular workload. Although there are no prospective clinical trials demonstrating its efficacy to prevent SCD or disease progression in AC, β-blocker therapy is recommended for all patients with a definite diagnosis of AC regardless of symptoms and arrhythmic manifestations. Prophylactic use in genotype-positive but phenotype-negative individuals does not seem justified in the absence of clinical trials demonstrating a clear benefit for these patients.143

Recently, left cardiac sympathetic denervation, which is a recognized safe and effective antiarrhythmic surgical procedure in patients with channelopathies, has been proposed as adjuvant treatment in AC patients who have adrenergic-dependent ventricular tachyarrhythmias refractory to traditional β-blocker therapy. However, only anecdotal cases have been reported about the beneficial effects of such a treatment option.145

**Antiarrhythmic Drugs**

The available evidence indicates that AAD therapy does not confer adequate protection from SCD. Of the 132 AC patients with an ICD reported by Corrado et al.,133 64 (48%) had an appropriate ICD intervention during a follow-up of 39±25 months although 53 patients (53/64; 83%) were receiving AAD therapy (sotalol, amiodarone, or β-blockers) at the time of first ICD intervention.

According to current recommendations, AAD therapy should be considered to reduce the arrhythmia burden in symptomatic patients with frequent premature ventricular beats and nonsustained VT.143 Pharmacologic therapy is also useful as an adjunct therapy to catheter ablation and ICD to reduce VT recurrences and device discharges. Sotalol and amiodarone (alone or in combination with β-blockers) are the most effective drugs with a relatively low proarrhythmic risk.146,147

Long-term therapy with amiodarone is limited because of its extracardiac toxicity.

**Catheter Ablation**

Catheter ablation is reserved for AC patients with sustained monomorphic VT because of enhanced automaticity or scar-related macro-reentry circuit. Initial experience with VT
catheter ablation, using conventional electrophysiologic mapping and endocardial approach, resulted in high acute success rate followed by a high rate of recurrence.148-150 The most plausible explanation is that the progression of disease leads to worsening fibrofatty myocardial replacement, which, in turn, creates new scar areas and reentry circuits over time. In addition, because the lesion wavefront characteristically initiates and progresses from the epicardium to the endocardium, several VT reentry circuits are located in the epicardial layer of the RV wall and are unapproachable from the traditional endocardial side. This may account for the better results of catheter ablation obtained with the epicardial approach via the pericardial space. In addition, more sophisticated mapping systems with 3-dimensional electroanatomic reconstruction of the RV geometry provide a clearer delineation of scar regions underlying the macro-reentry circuit of VT.151–153 However, VT recurrences during follow-up remain relatively high, a finding that is explained by the progressive nature of the myocardial substrate.153

According to the 2015 ITF consensus document, catheter ablation is recommended in the presence of incessant VT or frequent episodes of VT triggering ICD interventions, which are refractory to maximal pharmacological therapy including amiodarone.143 The epicardial approach is recommended after failure of endocardial ablation, although an initial combined approach (endo-epicardial) is reserved for centers with experience in epicardial procedures. Because catheter ablation is not a definitive therapy, it should not be considered as an alternative strategy to ICD for prevention of SCD.143

ICD Therapy
Randomized trials to guide ICD therapy in AC patients are not available for ethical reasons, low disease prevalence, and low event rates. However, data collected from observational registries consistently demonstrate the efficacy of ICD therapy to interrupt potentially fatal ventricular tachyarrhythmias.125,136–138,140 Moreover, projected survival curves based on lifesaving interventions of the device for potentially lethal arrhythmic events suggest that ICD offers the potential to improve survival in high-risk AC patients.123,136,138

In a recent meta-analysis reporting data of ≈600 AC patients who were at high risk and received an ICD, both for primary and secondary preventions, the estimated annual rate of cardiac death was 0.9%.154 However, there was a considerable ICD-related morbidity because of a high rate of device and electrode-related complications (4.4% per year) and inappropriate ICD interventions (3.7% per year).154 Therefore, the indications for ICD therapy should be the result of a balanced evaluation of the arrhythmic patient’s profile and the potential risk of device-related complications.

Difficulties in ICD lead placement into the RV and loss of sensing/pacing function during follow-up are both related to AC pathobiology, which is characterized by progressive myocardial loss and fibrofatty replacement. The incidence of inappropriate ICD discharges, mostly because of supraventricular tachyarrhythmia, can be reduced by appropriate ICD programming and administration of β-blockers. Although the use of dual-chamber detection algorithms offers the potential to decrease the number of inappropriate interventions by improving differentiation of ventricular from supraventricular arrhythmias, an additional lead in the atrium predisposes to a higher incidence of early and late post-operative complications.143

With regard to indications for ICD implantation, the 2015 ITF Consensus Statement on treatment of AC defined 3 categories of risk, based on the estimated annual rates of malignant arrhythmic events (Figure 6).144 The high-risk category (estimated event rate >10% per year) includes either patients with a history of cardiac arrest or sustained VT or patients with severe dysfunction of the RV, LV, or both. The indication for ICD implantation in this subset of patients is a class I recommendation. The intermediate-risk category (estimated event rate of 1–10% per year) included patients with ≥1 risk factors and no previous malignant arrhythmic events. Indications for ICD therapy for primary prevention of SCD among these

Figure 6. Pyramid of risk and indications for implantable cardioverter defibrillator (ICD) therapy in arrhythmogenic cardiomyopathy. According to the available data on annual mortality rates associated to previous events and specific risk factors, the estimated risk of major arrhythmic events in the high-risk category (apex of pyramid) is >10% per year, in the intermediate-risk category (mid of pyramid) ranges from 1% to 10% per year, and in the low-risk category (base of pyramid) is <1% per year. The recommendations for ICD implantation for different categories of arrhythmic risk are based on the 2015 International Task Force consensus document on treatment of arrhythmogenic right ventricular cardiomyopathy (ARVC).143 LV indicates left ventricle; PVB, premature ventricular beats; RV, right ventricle; VF, ventricular fibrillation; and VT, ventricular tachycardia.
patients remain an area of uncertainty. An ICD can be recommended (class IIa) in the presence of major risk factors such as syncope, nonsustained VT, or moderate ventricular dysfunction; ICD therapy may also be considered (class IIb) in selected patients with ≥1 minor risk factors, in whom the arrhythmic risk is not sufficiently high or defined. Decisions to implant an ICD in these patients should be made on an individual basis by taking into account not only the statistical risk but also the general health, socioeconomic factors, the psychological impact, the patient’s values and preferences, and most importantly, the high rate of device-related adverse effects over time. Finally, prophylactic ICD implantation is not recommended (class III) in asymptomatic patients with no risk factors and in healthy gene carriers (low-risk category; event rate <10% per year).

**Heart Failure Treatment**

Pharmacological treatment (angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, and diuretics) is used in AC patients who develop RV or biventricular symptomatic dysfunction. In the absence of heart failure symptoms, empiric treatment with angiotensin-converting-enzyme inhibitors or angiotensin II receptor blockers may be considered based on extrapolation from heart failure therapy in other diseases.

Long-term oral antithrombotic therapy is indicated in patients with thromboembolic events or atrial fibrillation.

Heart transplantation is the final treatment option in case of either debilitating heart failure refractory to standard therapy or potentially lethal ventricular tachyarrhythmias, which are uncontrollable with AAD therapy and catheter ablation. A follow-up study reported post-transplant survival rates of 94% and 88% at 1 and 6 years, respectively.

**Potential Translational Therapies and Future Directions**

The complex pathogenesis of AC creates many opportunities for the investigation of pathogenesis and translational therapies targeting unique pathways to prevent or reverse cardiomyopathy and arrhythmia. Zebrafish has great potential for high-throughput screening of small molecules to treat cardiac dysfunction caused by desmosomal mutations, with extension of these results into murine models. Drugs to activate canonical Wnt signaling by blocking its negative regulator, GSK3β, seem to be effective in these models although applicability to humans with AC is limited by the possibility of causing cancer with activation of this pathway. PPARγ and PPARα are also targets for translational therapies, based on cellular models of disease. Once again, caution for treatment that would block the PPARs arises from their known role in treatment of hypertension, hyperlipidemia, and diabetes mellitus. Translational therapies that are restricted to the heart could compensate for the potential noncardiac effects of these strategies. Numerous approaches to either regenerate cardiac myocytes with cardiac stem cells or to harvest the beneficial factors produced by cardiac progenitor cells are rapidly moving into clinical trials to address various forms of cardiomyopathy. If these novel therapeutic approaches live up to the current expectation, they may have a role in the treatment of AC in the future, with or without cellular reprogramming to address specific molecular abnormalities involved in the disease pathogenesis. The close connection between cardiac desmosomes and the sodium channel complex provides additional opportunities to address both ventricular dysfunction and arrhythmias with targeted treatments. Extending beyond AC, many new drugs for cardiomyopathy are under investigation to inhibit nephrisin, to sensitize or improve the function of the cardiac sarcomere, or to block other neurohormones, such as p38-MAP. As these novel therapies evolve, they may find a role to treat AC in the future.

**Sources of Funding**

Dr Corrado and Basso are supported by TRANSCAN (Translation in Arrhythmogenic Cardiomyopathy) Strategic Research Grant CPDA133979/13, University of Padua, Italy; Target Projects 331/12, Regional Health System, Venice, Italy, and Registry for Cardio-cerebro-vascular Pathology, Veneto Region, Italy.

**Disclosures**

Dr Judge has served as an advisor to Alnylam, Pfizer, Invitae, MyoKardia, Eidos, and Glaxo Smith Kline. The other authors report no conflicts.

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