“Padua criteria” for diagnosis of Arrhythmogenic Cardiomyopathy 2020

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Arrhythmogenic Cardiomyopathy (ACM): ***this is the newest designation***

Denominations: arrhythmogenic cardiomyopathy (ACM); arrhythmogenic right ventricular dysplasia (ARVD); ARVC/dysplasia (ARVC/D); Left-dominant arrhythmogenic cardiomyopathy (LDAC); and Arrhythmogenic LV cardiomyopathy (ALVC).

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Domenico Corrado et al Diagnosis of arrhythmogenic cardiomyopathy: The Padua criteria, Int J Cardiol. 2020 Nov 15; 319:106-114. doi: 10.1016/j.ijcard.2020.06.005. PMID: 32561223 DOI: 10.1016/j.ijcard.2020.06.005

A. Dominant-Right, arrhythmogenic right ventricular dysplasia (ARVD); ARVC/dysplasia (ARVC/D) (ARVC) or Classic form. RV (Upgrade Marcus F et al 2010 Task Force Diagnostic Criteria)

I. ***Common Pathways:*** *Desmosome intercalated disk/ Ion Channel*

II. ***Genetic Variants:*** *PKP2, JUP, DSC2, DSG2, DSP, SCN5A*

III. ***Morph-functional ventricular abnormalities:***

By echocardiography, CMRI or angiography:

Major

- Regional RV akinesia, dyskinesia, or bulging plus one of the following:

- Global RV dilatation (increase of RV EDV according to the imaging test specific monograms for age and gender)
- Global RV systolic dysfunction (reduction of RVEF according to the imaging test specific monograms for age, sex, and BSA)

Minor

- Regional RV akinesia, dyskinesia or aneurysm of RVFW.

IV. ***Structural myocardial abnormalities***

By CE-CMR:

Major

- Transmural LGE (stria pattern) of ≥1 RV region(s) (inlet, outlet, and apex in 2 orthogonal views)

By EMB (limited indications):

Major

- Fibrous replacement of the myocardium in ≥1 sample, with or without fatty tissue

V. ***Depolarization abnormalities***

Minor

- Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V1 to V3)
- Terminal activation duration of QRS ≥55 ms measured from the nadir of the S wave to the end of the QRS, including R', in V1, V2, or V3 (in the absence of complete RBBB)

VI. ***Repolarization abnormalities***

Major

- Inverted T waves in right precordial leads (V1, V2, and V3) or beyond in individuals with complete pubertal development (in the absence of complete RBBB)

Minor

- Inverted T waves in leads V1 and V2 in individuals with completed pubertal development (in the absence of complete RBBB)
- Inverted T waves in V1, V2, V3 and V4 in individuals with completed pubertal development in the presence of complete RBBB.

VII. ***Ventricular arrhythmias***

Major

· Frequent PVCs (>500 per 24 hours), NS-VT or S-VT of LBBB morphology.

Minor

· Frequent PVCs (>500 per 24 hours), NS-VT or S-VT of LBBB morphology with inferior axis ("RVOT pattern") (**Corrado D, et al. How to evaluate premature ventricular beats in the athlete: critical review and proposal of a diagnostic algorithm. Br J Sports Med. 2019. pii: bjsports -2018 -100529. doi: 10.1136/bjsports -2018 -100529**.) (**Muser D, et al. Risk stratification of patients with apparently idiopathic premature ventricular contractions. A Multicenter International CMR Registry. JACC: Clinical Electrophysiology 2019. DOI: 10.1016/j.jacep.2019.10.01**5)

VIII. ***Family history/genetics***

Major

· ACM confirmed in a first-degree relative who meets diagnostic criteria

· ACM confirmed pathologically at autopsy or surgery in a first-degree relative

· Identification of a pathogenic or likely pathogenesis

ACM mutation in the patient under evaluation:

Minor

· History of ACM in a first-degree relative in whom it is not possible or practical to determine whether the family member meets diagnostic criteria

· Premature SCD (<35 years of age) due to suspected ACM in a first-degree relative

ACM confirmed pathologically or by diagnostic criteria in second-degree relative

B. Biventricular: Right and left

I) **Common Pathways:** Cytoskeleton, Sarcoplasmic Reticulum, Sarcomere, Ion Channel, mitochondria

II) **Genetic Variant:** PLN

C. LV Dominant left ALVC Left-dominant arrhythmogenic cardiomyopathy (LDAC) (New diagnostic criteria)

I) **Common Pathways:** Cytoskeleton, sarcoplasmic reticulum, sarcomere, ion channel, mitochondria

II) **Genetic Variants:** *Lamin* A/C gene *(LMNA), DSP, TMEM43, LDB3, Desmin, α-actin, BAG3, NKX2-5, RBM20, SCN5A, KCNQ1, KCNH2, TRPM4, Mitochondrial mutations*

Lamin A/C (LMNA) cardiomyopathy forms an important and increasingly recognized group within the broad spectrum of non-ischemic cardiomyopathies. LMNA cardiomyopathy typically presents with atrioventricular block followed by recurrent ventricular arrhythmias with a high tendency to progression to end stage heart failure. Lamin A/C gene mutations can be found in severe forms of ARVC. Dilated cardiomyopathy caused by lamin A/C gene (LMNA) mutation is complicated with atrioventricular (AV) conduction disturbances, malignant ventricular arrhythmias, and progressive severe heart failure. Lamin A/C gene should be added to desmosomal genes when genetically testing patients with suspected ARVC, particularly when they also have ECG evidence for conduction disease. (**Giovanni Quarta et al, Mutations in the Lamin A/C gene mimic arrhythmogenic right ventricular cardiomyopathy Eur Heart J. 2012 May;33(9):1128-36. doi: 10.1093/eurheartj/ehr451**.)

DSP

III) **Morph-functional ventricular abnormalities**

By echocardiography, CMRI or angiography:

Minor

· Global LV systolic dysfunction (depression of LV EF according to the imaging test monograms for age and sex, and BSA or reduction of echocardiographic global longitudinal strain), with or without LV dilatation (increase of LV EDV according to the imaging test specific monograms for age, sex, and BSA)

Minor

· Regional LV hypokinesia or akinesia of LV free wall, septum, or both

IV) **Structural myocardial abnormalities**

By CE-CMR:

Major

- LVLGE (stria pattern) of ≥1 Bull's Eye segment(s) (in 2 orthogonal views) of the free wall (subepicardial or midmyocardial), septum, or both (excluding septal junctional LGE)

V) **Depolarization abnormalities**

- Low QRS voltages (<0.5 mV peak to peak) in limb leads (in the absence of obesity, emphysema, or pericardial effusion) It is caused by decrease of LV myocardial mass by fibro - fatty replacement (**Segura-Rodríguez D et al, Myocardial fibrosis in arrhythmogenic cardiomyopathy: a genotype -phenotype correlation study. Eur Heart J Cardiovasc Imaging. 2020 Apr 1;21(4):378 -386**.) (**Hall CL, et al variants are associated with a distinctive clinical and immunohistochemical arrhythmogenic cardiomyopathy phenotype. Int J Cardiol. 2020 May 15; 307:101 -108**) (**Te Rijdt WP, et al.Myocardial fibrosis as an early feature in phospholamban p.Arg14del mutation carriers: phenotypic insights from cardiovascular magnetic resonance imaging. Eur Heart J Cardiovasc Imaging 2019; 20:92 -100**) (**Cipriani A, et al. Arrhythmogenic Right Ventricular Cardiomyopathy: Characterization of Left Ventricular Phenotype and Differential Diagnosis WithDilated Cardiomyopathy. J Am Heart Assoc. 2020 Mar 3;9(5): e014628**) (**De Lazzari M, et al.. Relationship between electrocardiographic findings and cardiac magnetic resonance phenotypes in arrhythmogenic cardiomyopathy. J Am Heart Assoc 2018;7:e009855**.)

VI) **Repolarization abnormalities**

- Minor

T-wave inversion(TWI) in V4-V6 in the absence of complete LBBB, (**Sen-Chowdhry S et al, Left -dominant arrhythmogenic cardiomyopathy: an under -recognized clinical entity. J Am Coll Cardiol. 2008 Dec 16;52(25):2175 -87**) (**Sen-Chowdhry S, et al. Clinical and genetic characterization of families with arrhythmogenic right ventricular dysplasia/cardiomyopathy provides novel insights into patterns of disease expression. Circulation 2007;115(13):1710 -20**.) (**Cipriani A, et al. Arrhythmogenic Right Ventricular Cardiomyopathy: Characterization of Left Ventricular Phenotype and Differential**

Diagnosis WithDilated Cardiomyopathy. J Am Heart Assoc. 2020 Mar 3;9(5): e014628.) (Corrado D, Basso C, Judge DP. Arrhythmogenic Cardiomyopathy. Circ Res 2017;121(7):784 -802.) (De Lazzari M, et al. Relationship between electrocardiographic findings and cardiac magnetic resonance phenotypes in arrhythmogenic cardiomyopathy. J Am Heart Assoc 2018;7: e009855.)

VII) **Ventricular arrhythmias:**

· Minor

Frequent PVCs (>500 per 24 hours), NS-VT or S-VT with a RBBB morphology (excluding the "fascicular pattern")

VIII) **Family history**

Major

· ACM confirmed in a first-degree relative who meets diagnostic criteria

· ACM confirmed pathologically at autopsy or surgery in a first-degree relative

· Identification of a pathogenic or likely pathogenic ACM mutation in the patient under evaluation:

Minor

· History of ACM in a first-degree relative in whom it is not possible or practical to determine whether the family member meets diagnostic criteria

· Premature sudden death (<35 years of age) due to suspected ACM in a first-degree relative

ACM: arrhythmogenic cardiomyopathy; BSA: body surface area; EDV: end diastolic volume; EF: ejection fraction; ITF: International Task Force; LBBB: left bundle branch block; LGE: late gadolinium enhancement; LV: left ventricle; RBBB: right bundle branch block; RV: right ventricle; RVOT: right ventricular outflow tract.