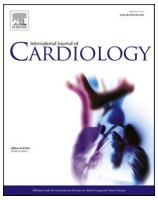
International Journal of Cardiology 395 (2024) 131447

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard



Proposed diagnostic criteria for arrhythmogenic cardiomyopathy: European Task Force consensus report☆

Domenico Corrado [a,1,*], Aris Anastasakis [b], Cristina Basso [a,1], Barbara Bauce [a,1], Carina Blomström-Lundqvist [c], Chiara Bucciarelli-Ducci [d], Alberto Cipriani [a], Carlo De Asmundis [e,1], Estelle Gandjbakhch [f,1], Juan Jiménez-Jáimez [g], Maria Kharlap [h], William J McKenna [i], Lorenzo Monserrat [j], James Moon [k,1], Antonis Pantazis [l,1], Antonio Pelliccia [m], Martina Perazzolo Marra [a], Kalliopi Pillichou [a,1], Jeanette Schulz-Menger [n,1], Ruxandra Jurcut [o,1], Petar Seferovic [p], Sanjay Sharma [q], Jacob Tfelt-Hansen [r,s,1], Gaetano Thiene [t], Thomas Wichter [u], Arthur Wilde [v,1], Alessandro Zorzi [a]

[a] Department of Cardio-Thoraco-Vascular Sciences and Public Health, University of Padua Medical School, Italy
[b] Unit of Inherited and Rare Cardiovascular Diseases, Onassis Cardiac Surgery Center, Athens, Greece
[c] Department of Cardiology, School of Medical Sciences, Faculty of Medicine and Health, Örebro University, Örebro, Sweden
[d] CMR services, Bromptom Royal Hospital, London, United Kingdom
[e] Heart Rhythm Management Centre, Postgraduate Program in Cardiac Electrophysiology and Pacing, Universitair Ziekenhuis, Brussel - Vrije Universiteit Brussel, Belgium
[f] Sorbonne Universitè, APHP, Centre de Référence des Maladies Cardiaques héréditaires Groupe Hospitalier Pitié Salpètrière-Charles Foix, Paris, France
[g] Cardiac Electrophysiology Center -University Hospital, Granada, Spain
[h] Department of cardiac arrhythmias, National Centre for Therapy and Preventive Medicine, Moscow, Petroverigsky, Russia
[i] Institute of Cardiovascular Science, University College London, United Kingdom
[j] Cardiovascular Genetics, Medical Department, Dilemma Solutions SL, A Coruña, Spain
[k] CMR Service, Barts Heart Centre, University College London, United Kingdom
[l] Inherited Cardiovascular Conditions services, The Royal Brompton and Harefield Hospitals, London, United Kingdom
[m] Institute of Sport Medicine and Science, Rome, Italy,
[n] Charité, Universitätsmedizin Berlin, Campus Buch – ECRC and Helios Clinics, DZHK Partnersite Berlin, Germany
[o] Expert Center for Rare Genetic Cardiovascular Diseases, Institute for Cardiovascular Diseases "Prof.dr.C.C.Iliescu", UMF "Carol Davila", Bucharest, Romania
[p] University of Belgrade, Faculty of Medicine and Heart Failure Center, Belgrade University Medical Center, Belgrade
[q] Cardiology Clinical Academic Group, St. George's, University of London, United Kingdom
[r] Section of Genetics, Department of Forensic Medicine, Faculty of Medical Sciences, University of Copenhagen, Denmark
[s] Department of Cardiology, The Heart Centre, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark
[t] University of Padua Medical School, ARCA Associazione Ricerche Cardiopatie Aritmiche ETS, Padova, Italy
[u] Dept. of Internal Medicine / Cardiology, Heart Center Osnabrück - Bad Rothenfelde, Niels-Stensen-Kliniken, Marienhospital Osnabrück, Osnabrück, Germany
[v] Amsterdam UMC location University of Amsterdam, Department of Cardiology, Amsterdam, the Netherlands

ARTICLE INFO

Keywords:
Cardiac magnetic resonance
Cardiomyopathy
Diagnosis
Ventricular arrhythmia
Sudden death

ABSTRACT

Arrhythmogenic cardiomyopathy (ACM) is a heart muscle disease characterized by prominent "non-ischemic" myocardial scarring predisposing to ventricular electrical instability. Diagnostic criteria for the original phenotype, arrhythmogenic right ventricular cardiomyopathy (ARVC), were first proposed in 1994 and revised in 2010 by an international Task Force (TF). A 2019 International Expert report appraised these previous criteria, finding good accuracy for diagnosis of ARVC but a lack of sensitivity for identification of the expanding phenotypic disease spectrum, which includes left-sided variants, i.e., biventricular (ABVC) and arrhythmogenic left ventricular cardiomyopathy (ALVC). The ARVC phenotype together with these left-sided variants are now more appropriately named ACM. The lack of diagnostic criteria for the left ventricular (LV) phenotype has resulted in clinical under-recognition of ACM patients over the 4 decades since the disease discovery. In 2020,

☆ Endorsed by the European Reference Network for rare, low prevalence and complex diseases of the heart (ERN GUARD-HEART).

* Corresponding author at: Department of Cardiac, Thoracic and Vascular Sciences and Public Health, Via Giustiniani, 2, 35121 Padova, Italy.
E-mail address: domenico.corrado@unipd.it (D. Corrado).

[1] Member of the European Reference Network for rare, low prevalence and complex diseases of the heart: ERN GUARD-Heart.

https://doi.org/10.1016/j.ijcard.2023.131447
Received 12 September 2023; Received in revised form 10 October 2023; Accepted 13 October 2023
Available online 14 October 2023

the "Padua criteria" were proposed for both right- and left-sided ACM phenotypes. The presently proposed criteria represent a refinement of the 2020 Padua criteria and have been developed by an expert European TF to improve the diagnosis of ACM with upgraded and internationally recognized criteria. The growing recognition of the diagnostic role of CMR has led to the incorporation of myocardial tissue characterization findings for detection of myocardial scar using the late-gadolinium enhancement (LGE) technique to more fully characterize right, biventricular and left disease variants, whether genetic or acquired (phenocopies), and to exclude other "non-scarring" myocardial disease. The "ring-like' pattern of myocardial LGE/scar is now a recognized diagnostic hallmark of ALVC. Additional diagnostic criteria regarding LV depolarization and repolarization ECG abnormalities and ventricular arrhythmias of LV origin are also provided. These proposed upgrading of diagnostic criteria represents a working framework to improve management of ACM patients.

1. Introduction

Arrhythmogenic cardiomyopathy (ACM) is a heart muscle disease characterized by substitution of the ventricular myocardium by fibrous or fibrofatty scar tissue, predisposing to malignant ventricular arrhythmias and sudden cardiac death (SCD) [1,2]. The disease was initially designated as a arrhythmogenic right ventricular *dysplasia* because it was thought to be a congenital defect in the development of the right ventricular (RV) myocardium [3]. The subsequent discovery that the disease is frequently caused by genetic defects in the cardiac desmosomes has led to its recognition as a *cardiomyopathy* (arrhythmogenic right ventricular cardiomyopathy; ARVC) [2,4]. Insights arising from postmortem investigations, genotype–phenotype correlation studies and myocardial tissue characterization by contrast-enhanced cardiac magnetic resonance (CMR) have increased the awareness that the disease often involves the left ventricle (LV). Accordingly, the current

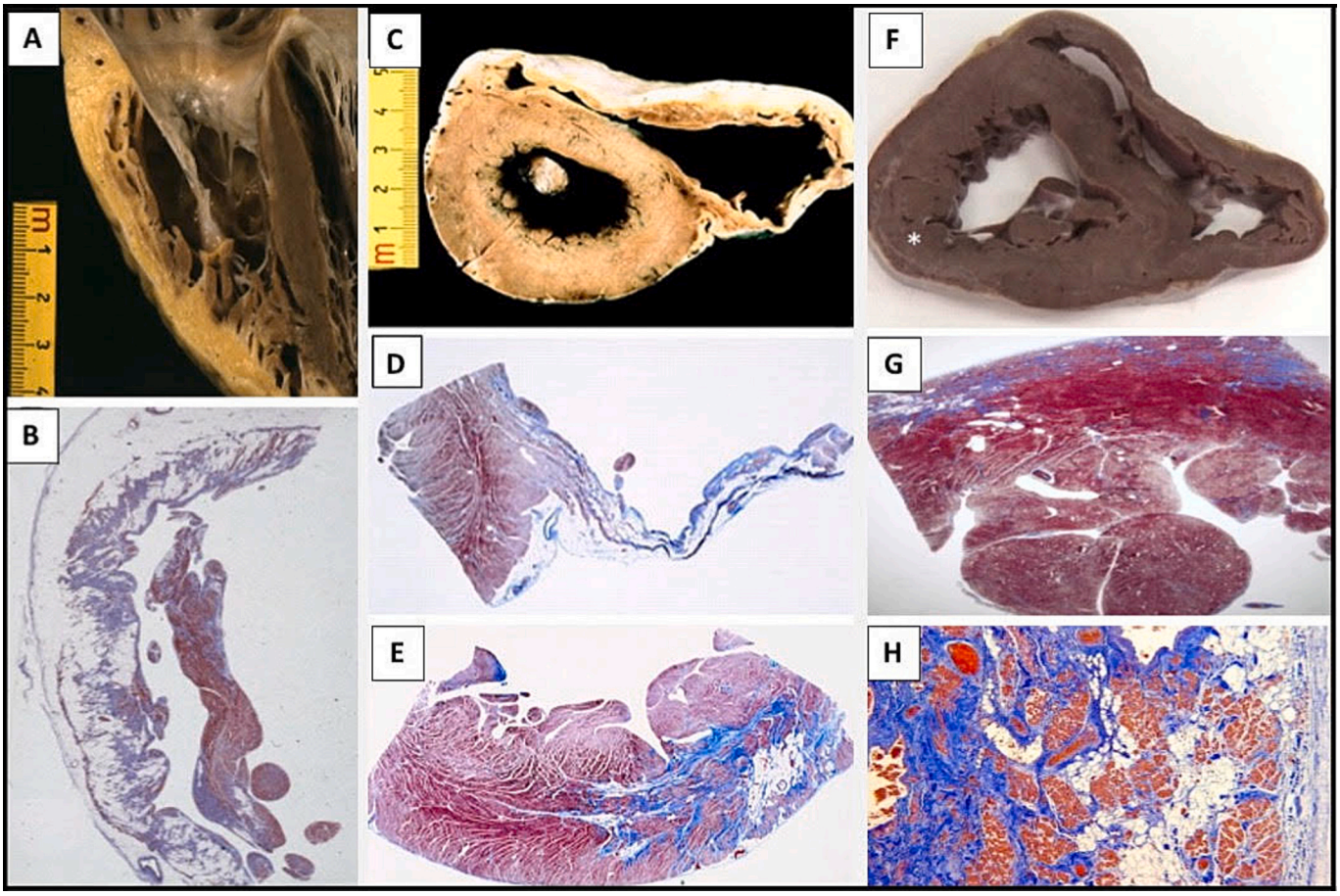


Fig. 1. Fibro-fatty myocardial scarring as a common pathologic myocardial lesion to the varieties of ACM phenotypes.
This figure shows that ACM is a distinctive cardiomyopathy whose fibro-fatty myocardial scarring represents the hallmark myocardial lesion and the arrhythmogenic substrate common to all the phenotypic disease variants (*Scarring/arrhythmogenic cardiomyopathy*).
ARVC phenotypic variant (A-B): Macroscopic longitudinal section of the heart showing apicobasal and transmural right ventricular myocardial scarring **(A)**. Panoramic histologic view of the RV free wall showing full-thickness myocardial loss with replacement by fibrous and fatty tissue, with residual myocardium confined to the endocardial trabeculae (trichrome stain).
ABVC phenotypic variant (C-E): Macroscopic transverse section of the heart showing infundibular and inferior subtricuspidal aneurysms **(C)**. Panoramic histological view of the inferior aneurysm showing wall thinning with transmural fibrofatty myocardial replacement (D). Panoramic histological view showing subepicardial fibro-fatty scar of the left ventricular free wall.
ALVC (dominant-left ARVC) variant (F–H): Macroscopic transverse section of the heart showing a whitish, thin, linear discoloration in the LV posterior-lateral wall (asterisk), involving the sub-epicardial and mid-mural myocardial layers. Histologic examination (boxed area) showing subepicardial/mid-myocardial fibrous (B) and fibro-fatty (C) myocardial replacement.

designation of 'arrhythmogenic cardiomyopathy' (ACM) better reflects the evolving concept of a "scarring" non-ischemic myocardial disease, either genetic or post-inflammatory, that may affect both ventricles, with some phenotypic variants being biventricular or left-dominant (Fig. 1) [5].

1.1. Historical overview on diagnostic criteria

Arrhythmogenic cardiomyopathy diagnostic criteria were first proposed in the 1994 and revised in the 2010 by an international Task Force (TF) [6,7]. Although these criteria demonstrated good accuracy for the original ARVC phenotype, they lacked sensitivity for left-sided disease variants. A 2019 International Expert report appraised of the clinical performance of the 2010 international TF criteria, identifying some diagnostic flaw and potential areas of improvement [4]. These included: 1) the lack of diagnostic criteria for diagnosis of the broader disease phenotypic spectrum, including biventricular and left ventricular ACM variants; and 2) the absence of tissue characterization by CMR using the late-gadolinium enhancement (LGE) technique. The CMR technique has progressively emerged as a clinically useful modality for assessing structural myocardial abnormalities in ACM, particularly for left-sided variants. Under the auspices of the Heart Rhythm Society (HRS), another group of experts published a consensus statement to guide physicians on evaluation and management of ACM, including clinically relevant information on genetics and disease mechanisms [8]. Both documents agreed that the 2010 TF criteria underrecognized a sizeable proportion of ACM patients with LV involvement [4,8]. In recent years, the increasing use of contrast-enhanced CMR has led to the recognition of an increasing number of individuals and families with predominantly biventricular or left-dominant phenotypes. Both documents drew attention to the limited availability of genetic, diagnostic and prognostic data for left-sided ACM, and highlighted the importance of defining diagnostic criteria for guiding experimental and clinical studies aimed to characterize the etiology/pathogenesis and the clinical outcome of these disease variants [4,8,9]. In 2020, an International expert consensus document provided upgraded diagnostic criteria for ACM (the "Padua Criteria"), which covered the entire disease phenotype spectrum [10]. The Padua criteria were derived from the diagnostic approach to ACM, which has been developed over 30 years by the multidisciplinary team of basic researchers and clinical cardiologists of the Medical School of the University of Padua. The present European TF report has been proposed by a large panel of European experts on ACM, who reviewed and refined the Padua diagnostic criteria, providing an upgraded and internationally recognized consensus document.

1.2. Rationale for upgraded diagnostic criteria

Given the increase awareness of the importance to diagnose left-sided variants of ACM, the growing recognition of the diagnostic value of CMR for detection of myocardial LV LGE/scar and the additional diagnostic role of LV ECG criteria and ventricular arrhythmias of LV origin, it was an urgent need to gather internationally recognized experts to revise and standardize the clinical diagnosis of the entire phenotypic spectrum of ACM. The proposed criteria represent a concrete implementation of the improvements suggested by the 2019 International Expert report [4] and a refinement of the 2020 Padua criteria [10], with particular reference to the identification of non-genetic diseases (phenocopies) that may fulfill the diagnostic criteria for ACM, mostly left-sided variants.

The criteria were developed by a European TF of internationally recognized experts in the basic and clinical aspects of ACM, who convened in a devoted Consensus Conference under the auspices of the European Reference Network for rare, low prevalence and complex diseases of the heart (ERN GUARD-Heart). All panelists were given the task to review the literature using PubMed and cover all topics related to a defined diagnostic work up, which then were presented and collegially discussed in the conference. The criteria were revised and standardized for the clinical diagnosis of the entire phenotypic spectrum of ACM on the basis of the current scientific evidence and the expert consensus. To reach consensus, the conference panelists voted on each diagnostic criterion. A threshold of 80% approval with a quorum of two-thirds of the panel was required. An initial failure to reach consensus was resolved by subsequent discussions, revisions as needed, and re-voting.

2. Diagnostic criteria

ACM is a cardiomyopathy that affects the RV, the LV or both ventricles and includes the following phenotypic variants: (i) the classic ARVC phenotype (also referred to as "*dominant-right*" phenotype), characterized by RV involvement with no detectable LV abnormalities; (ii) the *arrhythmogenic biventricular cardiomyopathy* phenotype, characterized by the involvement of both RV and LV (ABVC); and (iii) the

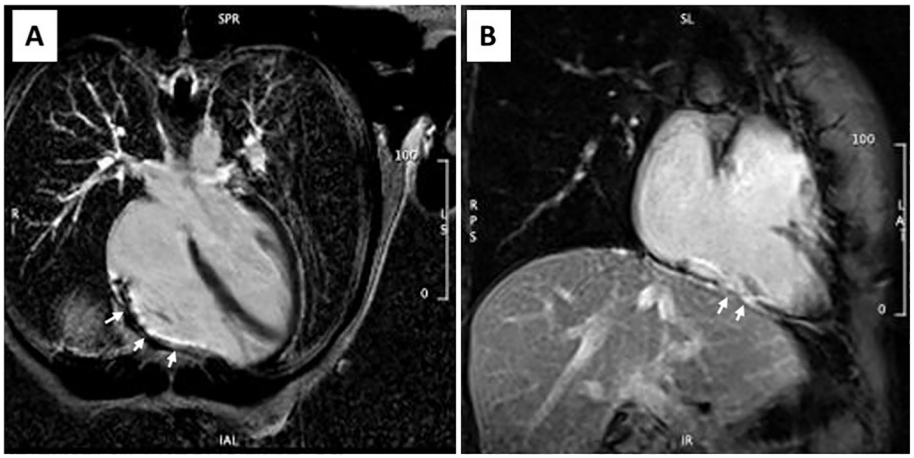


Fig. 2. LGE/myocardial fibrosis in ARVC (right-dominant ACM) phenotype.
CMR images of a 21-year-old patient with a pathogenic PKP-2 gene variant. Post-contrast images showing LGE/fibrous replacement of RV diaphragmatic free wall in the long-axis 4-chamber view (A, open arrows) and RV anterolateral wall in the sagittal view (B, solid arrows). On T1- weighted images, fatty infiltration in the same regions (not shown). On cine sequences, RV dilatation and regional akinesia (not shown).
ACM, arrhythmogenic cardiomyopathy; ARVC, arrhythmogenic right ventricular cardiomyopathy; CMR, cardiac magnetic resonance; RV, right ventricle; LGE, late gadolinium enhancement.

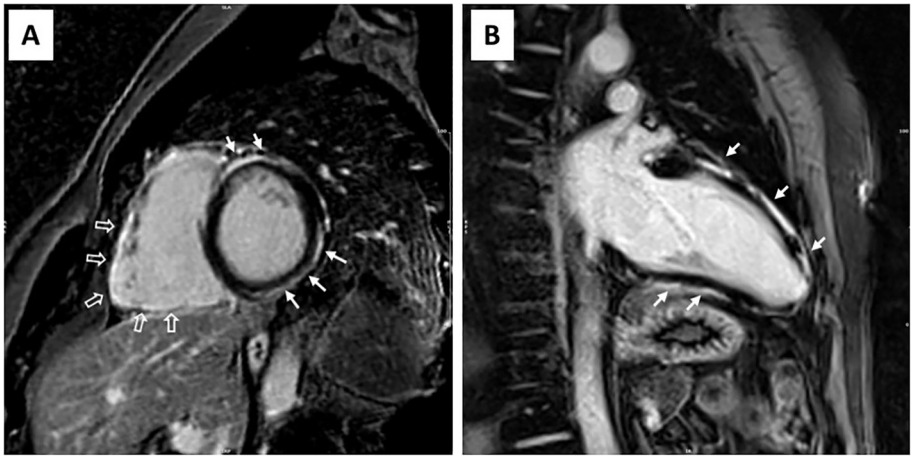


Fig. 3. LGE/myocardial fibrosis in Biv-ACM (biventricular ACM) phenotype.
CMR images of a 40-year-old patient with a pathogenic DSG-2 gene variant. Postcontrast images - short-axis view (A) and long-axis 2-chamber view (B) showing LGE/myocardial fibrosis in the basal anterolateral RV wall (open arrows) and anterior and inferior/inferolateral LV wall (solid arrows). On T1-weighted images no evidence of fatty infiltration (not shown). On cine sequences, RV regional akinesia with a mild reduction of the ejection fraction (i.e, 50%) and LV inferolateral hypokinesia with preserved systolic function (not shown).
ACM, arrhythmogenic cardiomyopathy; LV, left ventricle; RV, right ventricle; CMR, cardiac magnetic resonance; DSG-2, desmoglein-2 gene; LGE, late gadolinium enhancement.

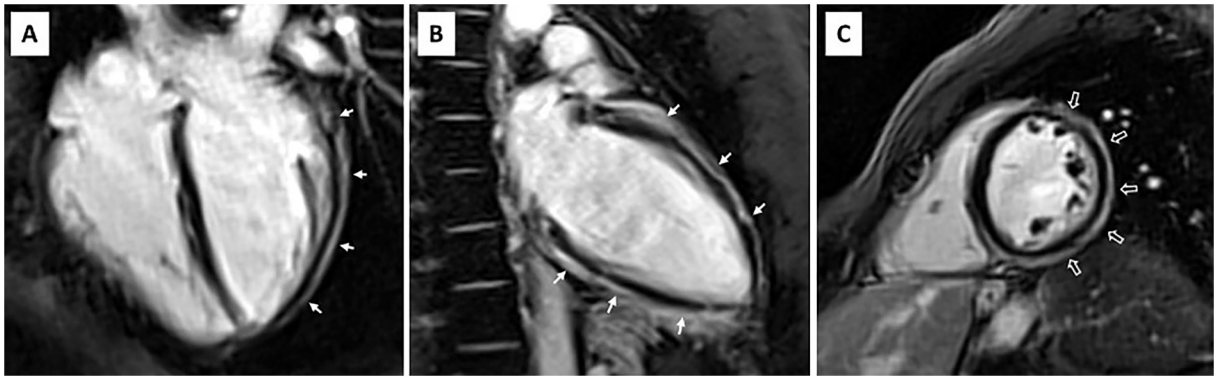


Fig. 4. LGE/myocardial fibrosis in ALVC (left-dominant ACM) phenotype. CMR images of a 24-year-old patient with a pathogenic DSP gene variant. Postcontrast images - long-axis 4-chamber view (A), and long-axis 2-chamber view (B) showing a large amount of LV subepicardial LGE (solid arrows), extending from basal-to-apical segments. Note the involvement of the LV free wall and septum with a "ring-like" pattern in the short-axis view (C, open arrows). On T1-weighted images no evidence of fatty infiltration (not shown). On cine sequences, normal cavity size and systolic function of both ventricles (not shown).
ACM, arrhythmogenic cardiomyopathy; ALVC, arrhythmogenic left ventricular cardiomyopathy; CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement.

arrhythmogenic left ventricular cardiomyopathy (ALVC) phenotype (also referred to as "*dominant-left*" phenotype), characterized by LV involvement with no detectable RV abnormalities (Figs. 2–4).

Similar to the previous 1994, 2010 and the 2020 "Padua criteria" scoring systems, the diagnosis is based on a multi-parametric approach encompassing 6 categories: 1) morphological and functional ventricular abnormalities; 2) structural myocardial abnormalities based on tissue characterization findings; 3) depolarization- and 4) repolarization electrocardiographic alterations; 5) ventricular arrhythmias; and 6) familial/genetic background [6,7,10]. The embedding of LGE for detection of myocardial scar by CMR tissue characterization with the identification of ACM phenotypic variants is crucial and the most important novelty, while the remaining updates are diagnostic refinements [11–24].

Table 1 reports the criteria for diagnosis of both the RV (left column) and LV (right column) involvement by each category.

2.1. Morpho-functional abnormalities

The morpho-functional abnormalities can be detected with echocardiography, CMR or ventricular angiography. Multidetector computer tomography (MDCT) also allows an accurate evaluation of ventricular volumes and function as well as identification of myocardial fatty tissue.; it may be useful for diagnosis when CMR is contraindicated because of claustrophobia, non-CMR-conditional ICD, or frequent arrhythmias [25].

Of importance, morpho-functional ventricular abnormalities should be evaluated using a comprehensive multimodality imaging approach and the imaging findings integrated into the clinical context [26].

For diagnostic specificity, the *major* RV morpho-functional criterion requires that global RV dilatation (based on sex specific volumetric measurements and indexed to body surface area) or RV systolic dysfunction has to be associated with major regional wall motion abnormalities (i.e. akinesia, dyskinesia, aneurysm, or bulging) [7]. The use of current reference values for cardiac chamber size and function

Table 1
European Task Force criteria for diagnosis of Arrhythmogenic Cardiomyopathy.

Category	RV Phenotype	LV Phenotype
I. Morpho-functional ventricular abnormalities	***Major*** • Regional RV akinesia, dyskinesia, or aneurysm *plus* one of the following: • global RV dilatation (increase of RV EDV according to the imaging test specific nomograms for age, sex and BSA)* or • global RV systolic dysfunction (reduction of RV EF according to the imaging test specific nomograms for age and sex)* ***Minor*** • Regional RV akinesia, dyskinesia or aneurysm of RV free wall	***Minor*** • Global LV systolic dysfunction, with or without LV dilatation (increase of LV EDV according to the imaging test specific nomograms for age, sex, and BSA)*
II. Structural alterations	***Major*** • Fibrous replacement of the myocardium in ≥1 sample, with or without fatty tissue, at histology ***Minor*** • Unequivocal RV LGE (confirmed in 2 orthogonal views) in ≥1 RV region(s) (excluding tricuspid valve)	***Major*** • "Ring-like" LV LGE (subepicardial or midmyocardial stria pattern) of ≥3 segments (confirmed in 2 orthogonal views), ***Minor*** • LV LGE (subepicardial or midmyocardial stria pattern) of 1 or 2 Bull's Eye segment(s) (in 2 orthogonal views) of the free wall, septum, or both (excluding patchy, focal or septal junctional LGE**)
III. Repolarization abnormalities	***Major*** • Negative T waves in right precordial leads (V_1, V_2, and V_3) or beyond in individuals ≥14 year-old (in the absence of complete RBBB and not preceded by J-point/ST-segment elevation) ***Minor*** • Negative T waves in leads V1 and V2 in males ≥14 year-old (in the absence of RBBB and not preceded by J-point/ST-segment elevation) • Negative T waves beyond V3 in the presence of complete RBBB • Negative T waves beyond V3 in individuals <14 year-old	***Minor*** • Negative T waves in left precordial leads (V_4-V_6) (in the absence of complete LBBB)
IV. Depolarization and conduction 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)	***Major*** • Low QRS voltages (<0.5 mV peak to peak) in all limb leads in the absence of other causes (e.g. cardiac amyloidosis, obesity, emphysema, or pericardial effusion)
V. Arrhythmias	***Major*** • Frequent ventricular extrasystoles (>500 per 24 h), non-sustained or sustained ventricular tachycardia of LBBB morphology with non-inferior axis ***Minor*** • Frequent ventricular extrasystoles (>500 per 24 h), non-sustained or sustained ventricular tachycardia of LBBB morphology with inferior axis ("RVOT pattern") • History of cardiac arrest due to ventricular fibrillation or sustained ventricular tachycardia of unknown morphology	***Minor*** • Frequent (>500 per 24 h) or exercise-induced ventricular extrasystoles with a RBBB morphology or multiple RBBB morphologies (excluding the "fascicular pattern") • Non-sustained or sustained ventricular tachycardia with a RBBB morphology (excluding the "fascicular pattern") • History of cardiac arrest due to ventricular fibrillation or sustained ventricular tachycardia of unknown morphology
VI. Family history/genetics	***Major*** • Identification of a pathogenic ACM-gene variant in the patient under evaluation • ACM confirmed in a first-degree relative who meets diagnostic criteria • ACM confirmed pathologically at autopsy or surgery in a first-degree relative ***Minor*** • Identification of a likely-pathogenic ACM-gene variant in the patient under evaluation • 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 confirmed pathologically or by diagnostic criteria in second-degree relative	

Note best practice is to use a reference range derived using the diagnostic approach and the same segmentation method as for patients. 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.

* Cut-off values of EDV and EF of the European TF criteria for respectively RV dilatation and systolic dysfunction are reported in Table 2.

** Septal junctional LGE at the RV insertion points.

(normalized for sex, age, body surface area) [27], and specific reference values for athletes [28], are recommended. Best practice is to use reference ranges derived from the same diagnostic tool and the applied segmentation method as that used in the patient (Table 2).

A proportion of ARVC patients do not show increased RV volume and/or decreased systolic function [19,22,24]. This finding reflects the segmental nature of myocardial scar areas that may not compromise the global hemodynamics of the RV. For this reason, the presence of RV wall motion abnormalities alone (i.e., in the absence of global RV dilatation/dysfunction) has been introduced as a *minor* criterion [19–22,24]. It should be recognized that the diagnostic accuracy of RV wall motion abnormalities may be limited by the potential misinterpretation (either over-or underdiagnosis) because of inherently imperfect subjective evaluation of cine-CMR images of the RV and the potential pitfall of non-

Table 2
Ventricular dilatation and systolic dysfunction by CMR (nomograms for age, sex, and BSA).

Right ventricular dilatation and systolic dysfunction			
	Women	Men	Athletes
EDV/ BSA (ml/m^2)	>112	>121	>130
EF (%)	<51	<52	<52

Left ventricular dilatation and systolic dysfunction			
	Women	Men	Athletes
EDV/BSA (ml/m^2)	>96	>105	>122
EF (%)	<57	<57	<58

CMR cutoff values of EDV and EF for non-athletes (+ or − 2 SD from the mean, respectively) derived from Petersen et al. [25] and for athletes (99%CI) from D'Ascenzi et al. [26]
The accuracy of nomograms is limited for children and elderly.
BSA, body surface area; EDV, end-diastolic volume; EF, ejection fraction.

pathologic RV wall motion alterations [9,29]. Demonstration of concomitant underlying LGE offers the potential to increase the diagnostic specificity of RV regional contractile alterations (see below).

Global LV systolic dysfunction (depression of LV ejection fraction or reduction of echocardiographic global longitudinal strain) and regional LV wall motion abnormalities (regional hypokinesia, akinesia or dyskinesia), with or without LV dilatation, are classified as *minor* morpho-functional criteria because of the low disease specificity for diagnosing left-sided ACM variants, given that these morpho-functional LV abnormalities can be seen in other common conditions such as ischemic heart disease. It is noteworthy that the ventricular remodeling of ALVC is often evidenced by echocardiography or cine CMR as a hypokinetic and non-dilated (or mildly dilated) LV ventricle [19,22,24,30].

2.2. Structural myocardial abnormalities

The structural myocardial abnormalities may be detected by CMR or endomyocardial biopsy (EMB).

Contrast-enhanced CMR offers the unique ability to identify LV LGE/myocardial scar (Supplementary Table 1). LGE needs to be ascertained well, typically with confirmation using two orthogonal planes or based on 3D-LGE-imaging or different approaches to exclude artifacts.

Although CMR has a low diagnostic sensitivity for LGE due to the thin RV wall and the suboptimal CMR resolution, demonstration of RV LGE may be useful for ACM diagnosis after exclusion of other scarring RV conditions, including ischemic heart disease or certain congenital heart disease such as Tetralogy of Fallot. Accordingly, the presence of LGE in at least one RV region on myocardial tissue characterization by CMR has been introduced as a *minor* RV criterion [24,31–34]. The combination of myocardial tissue characterization and the assessment of regional RV wall motion provides the best accuracy for diagnosing RV involvement by CMR, since the detection of an underlying LGE/myocardial scar on CMR increases the diagnostic specificity of RV wall motion abnormalities (and vice versa) [4,34].

LV LGE/myocardial scar occur earlier in the disease (pre detectable wall motion abnormalities) and may have a highly characteristic appearance which consists of non-ischemic LGE/myocardial scar affecting the subepicardial (less often the mid-myocardial) layers of the LV free wall, most often in the inferolateral region, with or without septal involvement [11–24,35]. Extensive LV LGE of ≥3 Bull's Eye segments, either contiguous in the same short-axis slice ("ring-like") or discontinuous is classified as *major* criterion because it is highly specific, while segmental LV LGE affecting 1 or 2 LV Bull's Eye segments (excluding not clinically relevant patchy, focal or septal junctional LGE) as *minor* [4,11,14–17,19]. The ring-like pattern of LGE is characteristically observed in ALVC caused by a genetic defects of *DSP*, *FLNC* or *PLN* (REF), although it could be also found in disease phenocopies [15,19,36].

LGE needs to be ascertained well, typically with confirmation using two orthogonal plans or based on 3D-LGE-imaging or different approaches to exclude artifacts.

Focal or patchy LV LGE is considered non-diagnostic and no clinically relevant in the absence of other abnormal findings. Of note, the pattern of "septal junctional" LGE at the RV insertion points, which is characterized by focal involvement of the inferior (or less frequently anterior) ventricular septum at the site of RV attachment, is excluded from the diagnosis of ACM because of its non-pathologic significance.

Fatty tissue can be detected with dedicated sequences by CMR (or by MDCT), and it is often observed in the same regions of LGE/scar. Although fatty tissue is not considered a diagnostic criterion when present alone, its combination with LGE increases the diagnostic specificity [34].

Electroanatomic voltage mapping may provide additional anatomic and electrophysiologic information on RV electroanatomic myocardial scar(s) in selected patients with inconclusive CMR "structural" findings [13,20,36,37]. The availability of advanced catheter technology (contact, high-density and omni-catheters) and the use of strict electrophysiologic criteria (evidence of contact confirmed by pacing and recording, identification of areas of contiguous electrogram abnormalities fulfilling established criteria for amplitude, width and fractionation and sampled at maximum 10 mm fill threshold) permit to minimize the risk of inaccurate interpretation of low-amplitude electrogram recordings in areas of normal myocardium [36]. The general consensus of the expert panel was to not recommend electroanatomic voltage mapping as a routine diagnostic tool, but to limit its use to patients undergoing electrophysiological study and catheter ablation of sustained VT, in whom the demonstration of reentrant VT mapped to a region of electroanatomic scar tissue may support the clinical diagnosis.

Because of the invasive nature with the inherent risk of complications, EMB is reserved to selected cases in whom the diagnosis (or exclusion) of ACM depends on histologic demonstration of replacement-type fibrosis, with or without fatty tissue (*major* structural criterion). EMB is a key test for the identification of non-genetic variants of ACM, such as isolated cardiac sarcoidosis, whose diagnosis relies on the histologic evidence of noncaseating epithelioid cell granulomas in the myocardium [38].

2.3. ECG repolarization abnormalities

Among the repolarization abnormalities, negative T wave in right precordial leads V1, V2 and V3 or beyond is a *major* criterion for ARVC in individuals with complete pubertal development (usually of age ≥ 14 years) (Fig. 5 A) [7,39–43]. Excluded are negative T-waves in V1 to V3 combined with J-point/ST-segment elevation due to early repolarization and those associated with complete RBBB secondary to the conduction defect.

Negative T waves in right precordial leads V1 and V2 are classified as a *minor* criterion for ARVC in males ≥14 year-old, in the absence of RBBB and J-point/ST-segment elevation. Negative T waves extending beyond V3 either in the presence of complete RBBB or in individuals <14 year-old is also a *minor* criterion. Of note, negative T waves extending from V1 to V5 or V6 can reflect a more severe RV dilatation with displacement to lateral leads, rather than expression of a concomitant LV disease [22]. Among the few ARVC patients who have an otherwise normal ECG and experienced ventricular arrhythmias, the most prevalent nonspecific abnormality was T-wave inversion in ≥2 of 3 inferior leads [44]. However, this ECG pattern may be observed in the normal population and in other heart diseases and it was not included among the present diagnostic criteria because of its low disease specificity.

The presence of isolated negative T waves in left precordial leads (V4–V6), with or without involvement of inferior leads, in the absence of

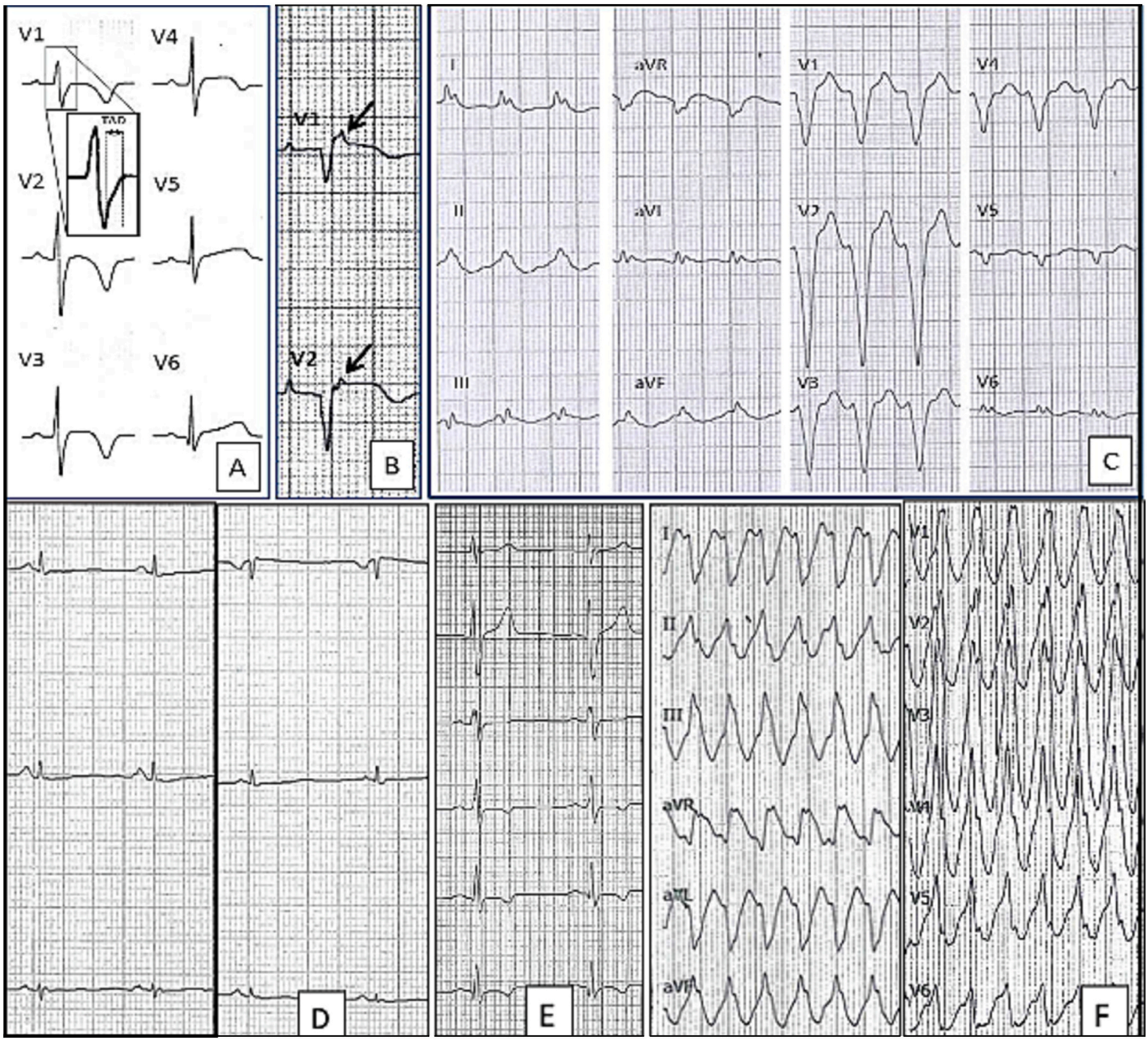


Fig. 5. Electrocardiographic abnormalities and ventricular arrhythmias in ACM variants.
(Top) ECG abnormalities and ventricular arrhythmias associated with the ARVC phenotype: negative T waves in leads V1 to V4 with prolongation of the right precordial QRS complex and delayed S-wave upstroke (the terminal activation duration, TAD, which is the interval between the nadir of the S wave and the end of all depolarization deflections, is prolonged, at 80 msec, in lead V1; the normal value is <55 msec.) (A); epsilon-wave in lead V1 (B); and ventricular tachycardia with a left bundle branch block morphology (C).
(Bottom) ECG abnormalities and ventricular arrhythmias associated with the ALVC phenotype: low QRS voltages (<0.5 mV) in the limb leads (arrow) (D), negative T-waves in leads V4 to V6 (arrows) (E), and ventricular tachycardia with a right bundle branch block morphology (F).
Adapted from Reference [2,30].

LBBB is a *minor* criterion for the LV phenotype (Fig. 5 E). The pattern shows limited specificity for the disease mostly in individuals of Afro-Caribbean ethnicity and among athletes [39,40,42].

2.4. ECG depolarization abnormalities

ECG markers of RV conduction disturbances (in the absence of RBBB) are considered *minor* criteria, which include prolongation of right precordial QRS duration with a delayed S-wave upstroke (terminal activation delay >55 ms) with or without QRS fragmentation and post-excitation epsilon waves (i.e., low-amplitude high frequency signals between end of QRS complex to onset of the T wave) (Fig. 5 A–B). [7] The "epsilon wave" pattern has been classified as *minor* criterion because it is largely influenced by ECG sampling rate and filtering and subject to a high interobserver variability [45].

A *major* criterion for LV involvement is the pattern of low QRS voltages in limb leads (<0.5 mV in all limb leads), which reflects the replacement of the sub-epicardial LV myocardium by scar tissue (in the absence of other potential causes such as cardiac amyloidosis, emphysema, pericardial effusion or obesity) (Fig. 5 D) [22]. It is rarely observed in healthy individuals and appears highly specific of LV myocardial scarring in patients with ACM [46]. It is noteworthy that inappropriate setting of low band-pass filters (<100 Hz) can cause spurious QRS voltage attenuation. Late potentials on signal averaged-

ECG are no longer considered, given their low diagnostic accuracy compared to modern diagnostic tests [4,47]. The majority of cardiological centers worldwide do not routinely employ this technique in the evaluation of patients with ACM [48]. However, SAECG may have a role for risk stratification of ACM through the identification of a potentially arrhythmogenic ventricular scar. This should be investigated by future studies correlating SAECG measurements of low amplitude late potentials of long duration with electroanatomic mapping-defined arrhythmogenic substrates, i.e., electroanatomic scars associated with a clinically documented sustained ventricular tachycardia [20].

2.5. Ventricular arrhythmias

According to the present European TF guidelines, ventricular arrhythmias need to be evaluated not only in terms of absolute number (i.e., premature ventricular beats (PVBs) >500/24 h) and complexity (non-sustained or sustained VT), but also with regard to the morphology of PVBs, that denotes the ventricular region for the origin of the arrhythmia (Fig. 5 C and F). Hence, it is clinically relevant to record the ventricular arrhythmia on 12- lead ECG by exercise testing or 12-lead 24-h Holter monitoring. Demonstration of PVBs, non-sustained or sustained VT with a LBBB and a non-inferior axis pattern has a greater disease-specificity (*major* ventricular arrhythmia criterion) than ventricular arrhythmia showing a LBBB/inferior axis morphology (*minor* ventricular arrhythmia criterion) as it indicates a RV outflow origin (RVOT) which is most often due to the idiopathic RVOT arrhythmia [4,49].

Several ECG scoring systems based on the QRS morphology during VT have been proposed for differential diagnosis [49–52]. Compared with idiopathic RVOT VT, in ARVC-related RVOT VT the QRS duration is longer (≥120 msec), QRS precordial transition is later (in V5 or V6) and QRS notching is more frequent. These QRS morphologic features are "site-dependent" rather than "disease-specific" and permit differentiation of free-wall from septal location of the RVOT VT, but not the identification of the underlying substrate, i.e., cardiomyopathic vs idiopathic. In selected patients, an electrophysiological study to test the inducibility of the clinical VT and/or multiple VT morphologies by programmed ventricular stimulation, or to demonstrate RV electroanatomic scar by electroanatomic voltage mapping may be useful for a differential diagnosis [32].

A RBBB morphology of either PVBs or VT may denote an origin from the LV [53]. The pattern of RBBB and superior axis with a broad QRS positive in V1 and late precordial transition to negative QRS (beyond V3) is often recorded in association with a LV scar involving the lateral or infero-lateral wall, as typically observed in patients with ABVC or ALVC [19,30,54]. Of note, PVBs with such a RBBB morphology, either monomorphic or associated with PVB of different morphologies, are typically induced by exercise testing in patients with left-sided ACM

Table 3
Different causes of Arrhythmogenic Cardiomyopathy.

ETIOLOGY		PHENOTYPIC VARIANT(S)	OTHER (POSSIBLE) PHENOTYPIC FEATURES
Genetic causes			
Desmosomal gene defects			
	PKP2 - Plakophilin C	ARVC	
	DSP - Desmoplakin	ALVC-BIV-ARVC	Subtle hair and skin abnormalities
	DSC2 - Desmocollin 2	ARVC-BIV	
	DSG2- Desmoglein 2	ALVC-BIV	
	Cardio-cutaneous syndromes		
	JUP-Plakoglobin (recessive)	ARVC-ALVC	Hair and skin abnormalities (Naxos disease)
	DSP-Desmoplakin (recessive)	ALVC	Hair and skin abnormalities (Carvajal disease)
Non-desmosomal gene defects (genocopies)			
	TMEM 43 (Transmembrane protein 43 - luma)	ARVC	High risk of SCD in males
	PLN (Phospholamban)	ALVC-BIV-ARVC	
	FLNC (Filamin C)	ALVC-BIV	Skeletal myofibrillar myopathy.
	DES (Desmin)	ALVC-BIV	Skeletal myofibrillar myopathy. Conduction system abnormalities
	LMNA (Lamin A/C)	ALVC-BIV	Skeletal muscular dystrophy. Sinus node dysfunction and conduction system abnormalities.
	TGFB3 (transforming growth factor-3)*	ARVC	
	CTNNA3 (alpha-T-catenin)*	ARVC	
	CDH2 (cadherin-2)*	ARVC	
	SCN5A (Sodium channel alpha unit)*	ARVC-ALVC	
	Neuromuscular disorders		
	DMD-Duchenne muscular dystrophy	ALVC	
	DMD-Becker muscular dystrophy	ALVC	
	DMPK-Myotonic dystrophy or Steinert	ALVC	Sinus node dysfunction and/or AV conduction abnormalities
Non-genetic causes (phenocopies)			
	Inflammatory		
	Post-acute or subacute/chronic viral myocarditis	ALVC	
	Cardiac sarcoidosis (chronic granulomatous myocarditis)	ALVC-BIV-ARVC	Multiorgan involvement. Conduction abnormalities (bundle branch block, bifascicular block and AV block)
	Auto-immune multisystem diseases (systemic lupus erythematous; polymyositis /dermatomyositis; scleroderma)	ALVC	Multiorgan involvement. Conduction abnormalities.Vasculitis.
	Parasitic infectious		
	Chagas disease	ARVC-BIV-ALVC	
Unknown cause			
	Idiopathic	ALVC-BIV-ARVC	

* Genes with limited evidence of ACM causality using the Clinical Genome Resource approach to gene-disease curation [56].

[55–61]. Other causes of exercise-induced, mostly polymorphic, ventricular arrhythmias include catecholaminergic polymorphic ventricular tachycardia or ischemic heart disease.

The presence of ventricular arrhythmias with a RBBB morphology at rest or during exercise is classified as a *minor* diagnostic criterion because of its low specificity not only for the underlying disease but also for the chamber of origin of the arrhythmia. Indeed, PVBs or VT with a RBBB morphology and early transition by V2 or even V3 has been mapped and ablated in the apical/inferior septal regions of a dilated RV [62].

Idiopathic "fascicular" arrhythmias characterized by a typical RBBB morphology and narrow (<130 ms) QRS are excluded from the diagnosis [47].

2.6. Family history/molecular genetics

Although the diagnostic criteria include the assessment of family history and molecular genetics, caution is recommended in the interpretation of the genotyping results in the light of the risk of misdiagnosis [63]. Misinterpretation of molecular genetic results is the consequence of our limited current understanding of the genetic basis of ACM and the high genetic noise, due to frequent disease-associated genetic variants both in the normal population and in other cardiomyopathies [64–66]. Moreover, preliminary data show that if molecular genetic findings are excluded from the diagnostic score the diagnostic yield is only reduced by 10% and does not impact the prognosis of ACM [67].

Accordingly, molecular genotyping is indicated to identify a pathogenic or likely pathogenic variant in a proband with phenotypic manifestations of ACM, followed by variant-specific cascade screening among family members for the detection of gene carriers at a preclinical stage [4].

The identification of a pathogenic ACM-gene variant according to the 2015 ACMG classification [68] is classified as *major* diagnostic criterion, while likely-pathogenic variant as a *minor* diagnostic criterion (Table 1). Genes with evidence of ACM causality according to the Clinical Genome Resource approach to gene-disease curation are reported in Table 3.

Family history criteria are also met if the disease is confirmed either pathologically or by diagnostic criteria in a first- degree relative (*major* criterion) or a second-degree relative (*minor* criterion). Premature SCD (<35 years old) due to suspected ACM in a first-degree relative is classified as a *minor* criterion [8].

3. Phenotypic variant

Because ACM is a structural heart disease rather than a genetic ion channel disorder, the diagnosis of any *phenotypically overt* ACM variant requires that at least one criterion, either major or minor, from category I (i.e., morpho-functional RV abnormalities) or II (i.e., structural RV abnormalities) is fulfilled in association with criteria from other categories. Pathogenic gene variants, ECG abnormalities or arrhythmias *alone* (i.e., in the absence of morpho-functional and structural criteria) can be observed in individuals, mostly family members, with "preclinical ACM" or "clinically concealed ACM". These recognized early stages are characterized by an incomplete development of the disease phenotype because of the lack of structural abnormalities (i.e., overt myocardial scarring) and/or morpho-functional alterations (i.e., regional or global systolic dysfunction), which are a prerequisite for a clinical diagnosis of ACM.

The diagnosis is considered "*definite*" when 2 major, 1 major and 2 minor, or 4 minor RV or LV diagnostic criteria from different categories are met. If morpho-functional and/or structural criteria are met for both ventricles, the patient is diagnosed with ABVC. A structural LV criterion (i.e., non-ischemic LV LGE), either major or minor, is required for diagnosis of ALVC. Non-definite diagnosis of ACM ("*borderline*" or "*possible*) is made in the presence of a lower total number of fulfilled diagnostic criteria (Supplementary Fig. 1). Patients with non-definite ACM should be followed-up to evaluate the possible disease progression over time to reach the criteria for a definite diagnosis.

4. Etiology

Pathogenic variants of genes encoding desmosomal proteins are the most frequent cause of inherited ACM, accounting for approximately 50% of probands [63]. The original ACM phenotype (and the derived diagnostic criteria for both right- and left-sided disease) is expressed by desmosomal gene-related disease (Fig. 6 A-B); however, it rarely may be reproduced by non-desmosomal genes defects ("genocopies"), including those associated with inherited neuromuscular disorders (Fig. 6 C–D) [69,70]. Moreover, a sizeable proportion of patients with non-genetic diseases, such as inflammatory cardiomyopathies including post-viral myocarditis and cardiac sarcoidosis as well as cardiomyopathies in the context of auto-immune multisystem diseases, may exhibit a phenotype which closely resembles that of inherited ACM ("phenocopies") and fulfils the diagnostic score (Fig. 6 *E*-F) [71,72]. Finally, the cause of the disease may be not-identifiable ("idiopathic" ACM) (Table 3).

The boundaries between these different etiologies may not be well demarcated. There is growing evidence of a complex interplay between genetic background and myocardial inflammation [73]. Inflammation in response to viral infection and/or immune triggers have been postulated to mediate/promote myocyte damage and death in genetic ACM. Acute myocarditis-like episodes with chest pain associated with ECG changes and troponin release may represent the initial clinical presentation and/or a disease progression modality (the so called "hot-phase") in patients with genetic ACM, mostly caused by pathogenic variants of DSP gene [74,75]. As a corollary, a non-ischemic myocardial scar found at CMR imaging evaluation after an episode of clinically overt acute myocarditis does not necessarily exclude a genetic etiology.

According to previous classifications of cardiomyopathies, where each phenotype is sub-classified into familial and non-familial forms and non-familial cardiomyopathies are further subdivided into acquired and idiopathic (not-identifiable cause) variants, both the HRS Expert Consensus Statement on Arrhythmogenic Cardiomyopathy [10] and the International Expert report [4], previously proposed an etiologic classification which under the large umbrella of 'arrhythmogenic cardiomyopathy' comprised a spectrum of conditions of different etiologies, either genetic or non-genetic, involving the RV, the LV or both, whose common denominator was the prominent non-ischemic ventricular myocardial scarring and the scar-related ventricular arrhythmias.

Beside the overlapping phenotype, the clinical rational of this proposed classification was that all etiologic variants are associated with a distinctively higher risk of arrhythmic SCD because myocardial scarring acts as a substrate of malignant ventricular arrhythmias. At variance with patients with DCM, in those presenting with ACM the implantation of an ICD for primary prevention should be considered, regardless of the etiology, earlier during the disease course when the systolic ventricular function is not yet severely depressed. [37,76]

Because of the diverse etiology, detection of a disease with phenotypic features fulfilling the diagnostic criteria for ACM should prompt a systematic search for the underlying cause. The identification of the specific cause is crucial because the clinical outcome, disease progression and the risk of SCD varies depending on the etiology [77–83]. The clinical work-up for identification of the specific etiology includes family screening, medical history (mostly for a prior "clinically proven" acute myocarditis), molecular genetic investigation, biochemical and metabolic laboratory, advanced imaging techniques and, in selected cases, endomyocardial biopsy. Family clinical screening followed by molecular genetic testing in case of proven or suspected inheritable disease is a key step to diagnose the genetic defect, either desmosomal or non-desmosomal, or to identify a familial but "gene elusive" condition. In the etiologic assessment may be of help to evaluate whether the disease is confined to the heart or occurs in the context of multiorgan involvement (for instance, neuromuscular diseases or sarcoidosis).

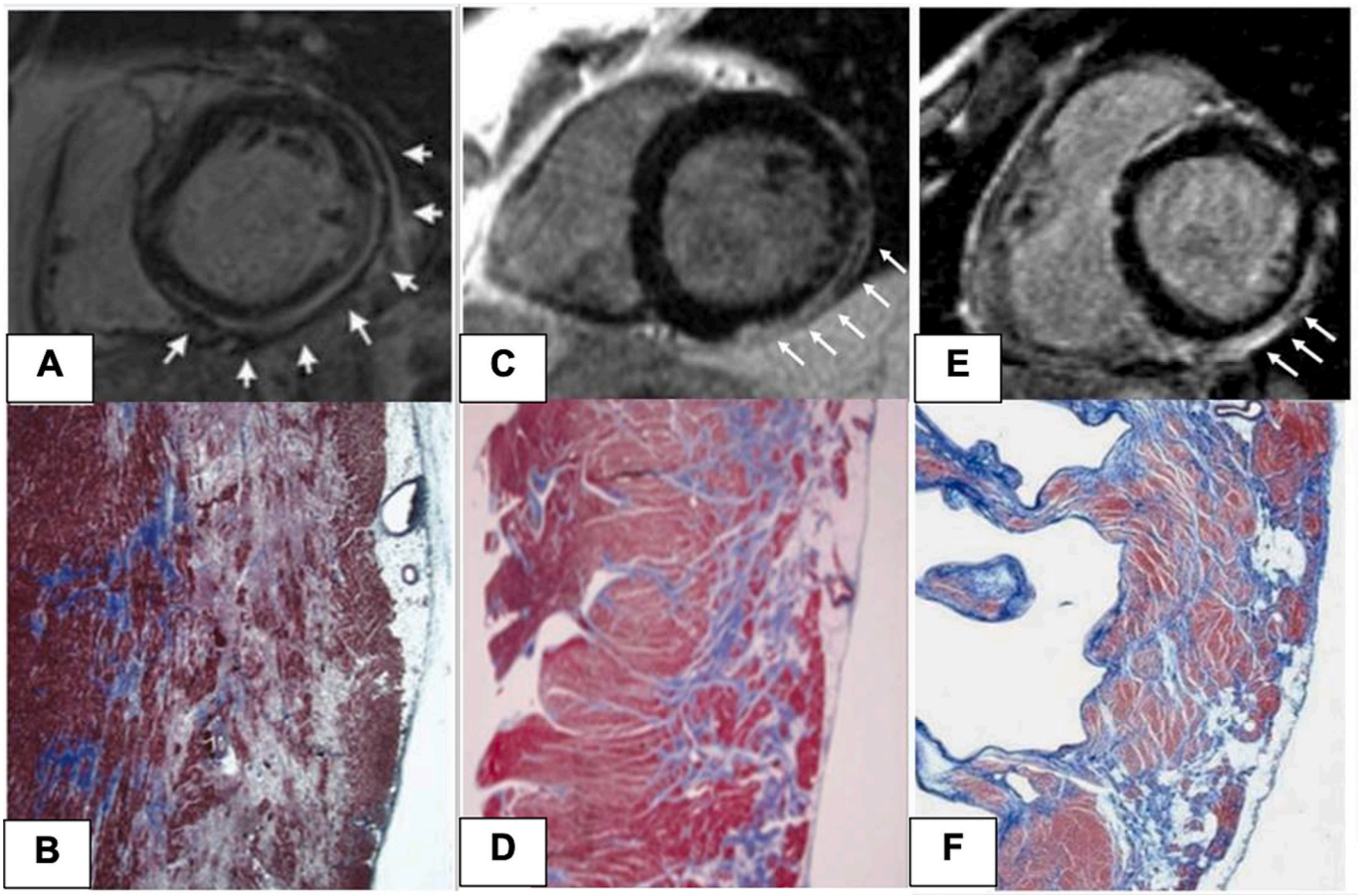


Fig. 6. Cardiac magnetic resonance features and histopathologic findings of arrhythmogenic left ventricular cardiomyopathy phenotype of different aetiologies. Desmosomal gene-related form (prototype disease phenotype): post-contrast T1 inversion recovery sequence in short-axis view showing subepicardial late gadolinium enhancement of the infero-lateral left ventricular wall in a DSP-gene mutation carrier (A). Panoramic histopathologic view showing fibro-fatty myocardial replacement of the outer layer of the infero-lateral left ventricular wall in a sudden cardiac death victim carrying a DSP-gene mutation (B). Muscular dystrophy variant (genocopy): post-contrast T1 inversion recovery sequence in short-axis view showing a subepicardial stria of late gadolinium enhancement in the left ventricular wall (white arrows) (C); corresponding panoramic histopathologic view of the inferolateral left ventricular wall showing replacement-type fibrosis confined to the outer-mid layer of the musculature (D). Post-myocarditis variant (phenocopy): post-contrast T1 inversion recovery sequence in short-axis view showing subepicardial late gadolinium enhancement of the inferolateral left ventricular wall (E); corresponding panoramic histopathologic view of the inferolateral left ventricular wall showing extensive fibro-fatty myocardial replacement in the subepicardial layer (F).
Adapted from Reference [4].

Targeted clinical work-up, based on disease-specific tests and diagnostic criteria is needed for etiologic characterization of some ACM phenocopies (for instance fludeoxyglucose uptake by positron emission tomography for cardiac sarcoidosis or serology for Chagas' disease). "Idiopathic" ACM is diagnosed in patients presenting with a disease phenotype which fulfils the diagnostic criteria but remains of unknown etiology after detailed clinical and genetic evaluation (Supplementary Fig. 2).

A number of "non-scarring" myocardial diseases or chest deformity may mimic some ACM features such as ventricular dysfunction/dilatation, *without fulfilling the diagnostic criteria* because they lack the prominent myocardial scarring which is the distinctive pathologic lesion of the disease. These differential diagnoses include: 1) congenital heart diseases such as left-to-right shunt due to atrial septal defects or partial anomalous pulmonary venous drainage leading to a RV volume overload; 2) conditions characterized by global ventricular dilatation/dysfunction unrelated to myocardial scarring such as pulmonary artery hypertension, athlete's heart or DCM; and 3) chest deformity such as pectus excavatum or carinatum and pericardial absence which may mimic ECG changes and imaging abnormalities [84].

Dilated cardiomyopathy is the most common condition requiring a differential diagnosis with ALVC. CMR imaging study permits to identify the main discriminant features between the two cardiomyopathies, which consist of different LV remodeling patterns, extent and regional distribution of myocardial fibrosis as evidenced by LGE, and relation between amount of LGE and LV systolic dysfunction [15,19–24]. LV myocardial scarring/LGE in patients with ALVC may replace up to 25–30% of the total LV mass, directly impacts on the reduction of LV systolic function and induces mild or no LV dilatation ("hypokinetic, non-dilated LV"). On the contrary, the extent of LV LGE in DCM ranges from patchy to absent (> 50% of cases) and is unrelated to the LV dilatation and systolic dysfunction ("non-scarring" cardiomyopathy) [15,19].

5. Clinical impact of upgraded diagnostic criteria

The lack of specific diagnostic criteria for left-sided variants of ACM has resulted in clinical under-recognition and under-treatment of patients with phenotypes other than the original ARVC over the four decades since the disease discovery [85]. Recent studies demonstrated that the limited sensitivity of 2010 TF criteria developed to diagnose the ARVC phenotype only, accounted for a significant proportion of missed diagnoses of ACM depending on the relative prevalence of ABVC and ALVC variants among study cohorts. In this regard, of 91 US patients

with *DSP*-related ACM, 49% with predominantly left-sided disease did not meet 2010 TF criteria, including 25% of those who experienced sustained ventricular arrhythmia or heart failure [81]. Moreover, of 679 p.Arg14del variant carriers with *PLN*-related left-sided ACM, 96% did not fulfill 2010 TCF criteria at baseline [80].

The available data confirm that this modern approach has the potential to substantially impact the diagnostic accuracy and permits a comprehensive identification of phenotypic varieties of ACM, mostly by the demonstration of LV LGE/myocardial scarring by post-contrast CMR sequences. The clinical impact of upgraded diagnostic guidelines including criteria for diagnosing the LV phenotype, was estimated by the "*post-hoc*" application of the previous 2020 "Padua criteria" scoring system to 112 patients diagnosed at the University of Padua over the period 2015–2019, using the 2010 TF criteria [9]. All patients fulfilled the criteria for *definite* ($N = 87$), *borderline* ($N = 15$), and *possible* ($N = 9$) ARVC. Of the 87 patients previously diagnosed with *definite* ARVC, 51 also fulfilled the new LV criteria, either morpho-functional or structural, and were re-classified as ABVC. Of 15 patients previously diagnosed with *borderline* ARVC, 5 were re-classified as definite ARVC because they met the RV LGE criterion and 6 as ABVC due to evidence of LV LGE. Of 9 patients previously diagnosed with *possible* ARVC based on the detection of a pathogenic desmosomal-gene variant (4 *DSP*, 3 *FLNC*, and 2 *DSG)* in the absence of RV morpho-functional and/or structural abnormalities, 7 were re-classified as ALVC because they met the LV structural (LV LGE) criterion [9].

The improvement of the diagnostic yield of ACM by the use of "Padua criteria" was also demonstrated in a pediatric cohort with involvement of the LV in half of the study sample [86].

Moreover, the incremental value of the diagnostic criteria was consistently confirmed among carriers of variants in *DSP*, *PNL* and *FLNC* genes, which are recognized left-sided variants-causing genes. In a pooled analysis of patients with *FLN*-related ACM, more than half of cases were diagnosed with definite ALVC according to the "Padua criteria", compared with the minority fulfilling the 2010 ITF criteria [87]. Of 72 probands with *DSP*-related ACM, the number of patients reaching a definite diagnosis of ACM using the "Padua criteria" versus the 2010 ITF criteria raised by 35% [88].

These data suggest that a better characterization of the disease phenotype leading to a substantial improvement of the diagnostic accuracy for ACM can be similarly obtained by using the proposed *new* European TF criteria which represent a refinement of the previous "Padua criteria" [10].

6. Terminology

The panelists of the present European TF consensus document were aware of the need to appropriately revise the disease terminology in order to formalize that ACM is a primarily "scarring" myocardial disease as a result of a myocyte death and fibro-fatty repair process, with scar-related ventricular arrhythmias and progressive impairment of ventricular systolic function which correlates with the amount of scar tissue replacement of the lost ventricular myocardium.

The appropriateness of the relatively non-specific designation "arrhythmogenic" cardiomyopathy has been rightly disputed. It has been argued that the term 'arrhythmogenic cardiomyopathy' encompasses all cardiomyopathies, as all cardiomyopathies are potentially arrhythmogenic. The adjective '*arrhythmogenic*' was first introduced by Marcus and Fontaine in their original report on a series of affected patients presenting with right ventricular tachycardia [3]. Hence, it refers to the propensity of the disease to induce ventricular arrhythmias in relation to the underlying myocardial scar tissue that acts as an *arrhythmogenic* substrate. The original disease nomenclature was maintained over decades for respect to the tradition and the pioneers of the disease (the missed Professors Guy Fontaine, Frank Marcus, Andrea Nava and Nicos Protonotarios) who coined this term. However, basic scientists and clinical cardiologists over time have used the term ACM thinking about a primarily "scarring" and secondarily "arrhythmogenic" heart muscle disease. Four decades later, the time has come to appropriately revise the terminology in order to emphasize the distinctive phenotype of the disease. The updated designation of "*scarring/arrhythmogenic cardiomyopathy*" [89], more specifically would reflect the hallmark pathobiological feature of the disease, namely the non-ischemic myocardial scarring, which is common to the phenotypic varieties of the disease (with involvement of RV, LV or both) and independent from the disease etiology, either genetic forms or phenocopies, and it allows differential diagnosis with "non-scarring" heart muscle disease such as dilated cardiomyopathy (or non-dilated LV cardiomyopathy) [90], in which the impairment of systolic function, with or without ventricular dilatation, is unrelated to myocardial fibrosis.

7. Conclusions

This European TF consensus document is intended to provide practical guidance and advice for a modern diagnostic approach to the entire phenotypic spectrum of ACM and is expected to improve the quality of care. A key upgrade of the proposed diagnostic approach was the recognition that a variety of phenocopies may meet the diagnostic criteria for the LV phenotype, originally expressed by desmosomal gene-related ACM, and need to be accurately identified because the prognosis, treatment and outcome may be etiology-dependent. The incorporation of myocardial tissue characterization by CMR for detection of myocardial scarring using the LGE technique is of added value for a more accurate diagnosis of the disease phenotype, with particular reference to ABVC and ALVC variants, and helps differential diagnosis with other "non scarring" myocardial diseases, with ensuing important prognostic and therapeutic implications. Novel diagnostic criteria regarding ECG abnormalities of LV depolarization/ repolarization and ventricular arrhythmias of LV origin are also updated and provided. The goal of upgraded criteria based on the expanding phenotypic and etiologic spectrum of ACM is to fill the diagnostic gap of the previous diagnostic guidelines and to provide a feasible codification for future translational and clinical research. Before these proposed European TF diagnostic criteria are routinely used of in the real-world clinical practice, their clinical utility needs to be further validated by future studies on patient populations with a variety of disease phenotypes of different etiologies.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2023.131447.

Fundings

The article was funded by the European Union-next generation EU-PNRRM6 C2-Investement 2.1 (PNRR-MR1-2022-12376614).

Acknowledgements

The authors thank the Fondazione Internazionale Menarini for supporting the project consensus conference.

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