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Contemporary diagnostic approach to arrhythmogenic cardiomyopathy: The three-step work-up

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ABSTRACT

Arrhythmogenic Cardiomyopathy (ACM) is a cardiac disorder characterized by non-ischemic myocardial scarring, which may lead to ventricular electrical instability and systolic dysfunction. Diagnosing ACM is challenging as there is no single gold-standard test and a combination of criteria is required. The first diagnostic criteria were established in 1994 and revised in 2010, focusing primarily on right ventricular involvement. However, in 2019, an international expert report identified limitations of previous diagnostic scoring and developed the 2020 Padua criteria with also included criteria for diagnosis of left ventricular variants and introduced cardiac magnetic resonance tissue characterization findings for detection of left ventricular myocardial scar. These criteria were further refined and published in 2023 as the European Task Force criteria, gaining international recognition. This review provides an overview of the 20 years of progresses on the disease diagnostic from the original 1994 criteria to the most recent 2023 European criteria, highlighting the evolution into our understanding of the pathobiology and morpho-functional features of the disease.

Introduction

Arrhythmogenic cardiomyopathy (ACM) is a cardiac muscle disorder characterized by the progressive replacement of ventricular myocardium with fibro-fatty tissue (1). This condition predisposes to life-threatening ventricular arrhythmias (VAs) leading to sudden cardiac death (SCD) and may cause systolic ventricular dysfunction with heart failure (2).

Originally believed to exclusively affect the right ventricle (RV), the earliest documented case of ACM as a heredo-familial disease dates back to 1728, when Giovanni Maria Lancisi reported a multi-generational recurrence of the disorder (3). In 1982, Marcus et al. coined the term "arrhythmogenic right ventricular dysplasia" following the examination of 24 adult patients exhibiting VAs with a left bundle branch block (LBBB) morphology, suggesting an origin in the affected RV (4). Back then, it was perceived as a developmental defect of the RV myocardium. Subsequently, Thiene et al. identified ACM as a primary cause of SCD in young Italian individuals and athletes (5): post-mortem examinations revealed histopathological evidence of inflammation, degeneration, and necrosis foci, indicating the development of the heart muscle disease post-birth. With the discovery of gene defects linked to desmosomal proteins, the term *dysplasia* was discarded in favor of "arrhythmogenic right ventricular *cardiomyopathy*" (ARVC). As a result, ACM was included among the WHO definition and classification of cardiomyopathies (5).

Evolution of diagnostic criteria: a historical overview

Due to the absence of a definitive gold standard for diagnosing ARVC, criteria were established in 1994 by a Task Force (TF) of experts in cardiomyopathies. The formal criteria encompassed multiple parameters grouped into six distinct categories, including global or regional dysfunction, imaging-detected structural alterations in RV, tissue characterization via endomyocardial biopsy (EMB), ECG repolarization abnormalities, ECG depolarization abnormalities, arrhythmias, and family history. Criteria were classified as "major" or "minor" based on their specificity in distinguishing

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ARVC from conditions with overlapping phenotypes, such as idiopathic right ventricular outflow tract (RVOT) ventricular tachycardia (VT) or biventricular dilated cardiomyopathy (DCM). Diagnosis required the presence of either 2 major criteria from different groups, or 1 major plus 2 minor criteria, or 4 minor criteria (6).

The 1994 TF criteria had several diagnostic limitations, as they were highly specific but lacked sensitivity for asymptomatic patients and early/minor ARVC cases. Indeed, the criteria were based on clinical experience and derived mostly from severe manifestations observed in SCD victims and symptomatic index cases. Additionally, the qualitative and subjective nature of assessing clinical parameters made practical application challenging.

In 2010, the revised International Task Force (ITF) criteria were introduced (7), maintaining the six-category organization and “major/minor” classification. To enhance diagnostic accuracy, quantitative imaging reference values were introduced to define normal RV and various degrees of structural and functional abnormality. A quantitative histomorphometric definition of fibrofatty myocardial replacement on EMB was also incorporated. Updates were made to the criteria for ECG and VAs, and the family history category included new molecular genetic information. Moreover, the 2010 criteria introduced a diagnostic “grading”, ranging from possible" (1 major or 2 minor criteria) and "borderline" (1 major plus 1 minor or 3 minor criteria) to “definite” diagnosis (2 major or 1 major plus 2 minor criteria or 4 minors).

Since 2010, research has greatly enhanced our understanding of the disease’s phenotypic manifestation. This led to recognizing that the disease most often involves the LV resulting into biventricular or left-dominant phenotypic variants. Consequently, the term "ARVC" has been replaced by that of "arrhythmogenic cardiomyopathy" (ACM), which better describes the broader phenotypic spectrum of the disease.

In 2019, a panel of International Experts in cardiomyopathies conducted an extensive critical review, highlighting three key observations regarding the 2010 criteria:

- The absence of specific criteria for diagnosing left-sided variants.
- The crucial role of cardiac magnetic resonance (CMR), not only in evaluating volumes, systolic function, and wall motion abnormalities, but particularly in tissue characterization using the late gadolinium enhancement (LGE) technique (8).
- The inclusion of genetic testing as a major diagnostic criterion, even in probands. This approach potentially enables a diagnosis in cases lacking morpho-functional ventricular abnormalities or tissue changes. In contrast, other cardiovascular diseases recommend genetic testing only in probands who meet clinical diagnostic criteria (9).

In addition to these observations, experts emphasized the need to revise the RV criteria. In the same year, an expert opinion document from the Heart Rhythm Society (HRS), was published with the aim to assist physicians in evaluating and managing ACM. This statement covered essential aspects, including genetics and disease mechanisms (10). This publication also recognized that the 2010 TF criteria inadequately identified a significant number of ACM patients with LV involvement.

Based on these critical evaluations, in 2020 a team of international experts proposed updated diagnostic criteria for ACM, named the "the Padua Criteria"(11). Most recently, in 2023 a group of internationally recognized experts in the basic and clinical aspects of ACM from different European countries 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). The criteria proposed by the above expert ERN Task Force, the “European Task Force criteria”, represented a refinement of the previous “2020 Padua criteria” and have been developed with the aim to improve the diagnosis of ACM with upgraded and internationally recognized criteria (12).

A novel aspect of this latter document is the characterization of ACM primarily as a "scarring" myocardial disease, stemming from myocyte death and fibro-fatty repair processes (13). This leads to scarring-related VAs and a progressive impairment of ventricular systolic function. The systolic dysfunction correlates with the extent of scar tissue replacing the myocardial loss. Hence, the expert consensus document proposed a more specific designation for the disease, namely "scarring/arrhythmogenic cardiomyopathy" which emphasizes the pivotal pathobiological disease feature consisting in non-ischemic myocardial scarring. This feature is consistent with all phenotypic variations of the disease involving the RV, LV, or both, and remains independent of the underlying etiology, encompassing genetic forms and phenocopies.

The European task force diagnostic criteria

Step 1: Criteria for RV and LV involvement

According to the European TF criteria, the classification of ACM includes the following phenotypic variants:

1. The *dominant-right variant* (ARVC), which is the classical phenotype primarily affecting the RV with any detectable LV structural abnormalities.
2. The *arrhythmogenic biventricular cardiomyopathy* (ABVC) phenotype, involving both RV and LV.
3. The *arrhythmogenic left ventricular cardiomyopathy* (ALVC) phenotype, also known as the dominant-left variant, which involves the LV with no structural abnormalities in the RV.

The European Task Force (TF) criteria are structured into two distinct sets to identify clinical indications of RV and LV involvement, respectively. Both sets maintain the traditional arrangement of 6 diagnostic categories (14). The criteria are categorized as either "major" or "minor" based on their specificity for diagnosing ACM, allowing consideration of only one major or minor criterion for each category (**Table 2S**).

1. **Morpho-functional ventricular abnormalities**
   Morpho-functional abnormalities can be identified through echocardiography, CMR, ventricular angiography or multidetector computer tomography (MDCT) as an alternative diagnostic method when CMR is not feasible (claustrophobia, non-CMR-compatible implantable cardioverter-defibrillator (ICD), or frequent arrhythmias) (15).
   To improve diagnostic specificity, the major morpho-functional criterion for the RV requires the presence of global RV dilatation or systolic dysfunction, along with regional wall motion abnormalities such as akinesia, dyskinesia, or aneurysm. It is recommended to use current reference values for cardiac chamber size and function, adjusted for factors such as sex, age, and body surface area, and specific reference value for athletes (16,17). Echocardiography is frequently chosen as the initial imaging method due to its widespread availability, non-invasiveness, and ease of repetition. It can offer insights into the cardiac phenotype, providing indications of disease etiology, morphology, hemodynamics, and severity. Importantly, the infero-basal (sub-tricuspid) RV region, a common site for wall motion abnormalities in ACM, is often neglected in standard echocardiographic views. Therefore, when ACM is suspected, an off-axis 2-chamber apical view focused on evaluating the inferior RV wall should be obtained (18). Additionally, a minor criterion now considers regional wall motion abnormalities in the absence of RV dilation or dysfunction. This acknowledges the localized nature of ACM, where localized fibro-fatty replacement can impact segmental contractility without significantly

affecting overall RV hemodynamics. However, it is categorized as a minor criterion due to potential misinterpretation, especially in CMR where pitfalls may arise from non-pathological wall motion abnormalities.

LV morpho-functional criterion is classified as minor due to limited specificity in diagnosing left-sided variants of ACM and includes global LV systolic dysfunction with or without LV dilatation. Their minor designation is due to limited specificity for left-sided variants, as similar LV abnormalities can occur in conditions like ischemic heart disease. Notably, ventricular remodeling in ALVC is often identified through echocardiography or cine- CMR, revealing a hypokinetic and non-dilated (or mildly dilated) LV ventricle (19).

2. **Structural myocardial abnormalities**

Fibrous or fibro-fatty replacement are typical of ACM and can be detected through CMR or EMB. Currently, CMR is recognized for its diagnostic specificity in revealing RV LGE, although its sensitivity is limited due to CMR technology's inherent characteristics, including suboptimal spectral resolution and a less-than-ideal contrast-to-noise ratio when quantifying the thin RV wall. Optimal specificity is achieved by assessing wall motion alterations alongside tissue characterization abnormalities. As a result, the presence of LGE in at least one RV region with CMR has been designated as a minor RV criterion (12).

LV LGE, indicating myocardial scar, appears early in ACM, preceding visible wall motion abnormalities. It exhibits a characteristic appearance in the subepicardial or occasionally mid-myocardial layers of the LV free wall, primarily in the inferolateral region and sometimes with septal involvement. Confirmation of LGE is crucial, requiring verification in two orthogonal planes or using 3D-LGE imaging to eliminate potential artifacts. Extensive LV LGE covering $\geq$3 Bull's Eye segments, either contiguous in the same short-axis slice ("ring-like") or discontinuous, is a major criterion due to high specificity. Segmental LV LGE affecting 1 or 2 LV Bull's Eye segments is considered minor. Patchy or focal LV LGE is considered non-diagnostic and lacks clinical relevance without other abnormal findings. Importantly, "septal junctional" LGE at RV insertion points is excluded from ACM diagnosis due to its non-pathologic significance (19,22,23). While the presence of fatty tissue alone is not a diagnostic criterion, its identification using dedicated sequences by CMR or MDCT in regions of LGE/scar enhances diagnostic specificity (20).

Electroanatomic voltage mapping, not usually recommended for diagnosis, may enhance sensitivity for RV myocardial scars in selected patients undergoing electrophysiological study and catheter ablation for sustained VT (21,24).

Because of its invasive nature and associated risks, EMB is selectively recommended in cases where the diagnosis or exclusion of ACM hinges on histologic evidence of replacement-type fibrosis, with or without fatty tissue (major structural criterion). EMB becomes especially critical in identifying non-genetic variants of ACM, like isolated cardiac sarcoidosis, where the diagnosis relies on histologic confirmation of noncaseating epithelioid cell granulomas in the myocardium (25).

3. **ECG repolarization abnormalities**

The identification of T-wave inversion (TWI) in right precordial leads (V1–V3) or beyond is a major criterion, while TWI limited to V1–V2 is a minor criterion, both for RV involvement. These observations require the absence of complete right bundle branch block (RBBB) and J-point/ST-segment elevation due to early repolarization. In the presence of RBBB, TWI beyond V3 is considered a minor criterion. These criteria are applicable to individuals who have completed pubertal development, typically around the age of 14. For individuals younger than 14, TWI beyond V3 is a minor criterion (26). It is crucial to note that the extension of TWI from right precordial leads (V1–V3) to left ones (V4–V6) indicates more severe RV dilatation rather than LV involvement (27). The prediction of LV involvement can only be made with TWI in left precordial leads (V4–V6) in the absence of complete left bundle branch block (LBBB), but it is considered a minor criterion due to its low specificity (28).

4. **ECG depolarization and conduction abnormalities**

The signal-averaged ECG is no longer considered in the criteria, as experts believe it lacks specificity and has low diagnostic accuracy. However, it may still have a role for risk stratification by identifying potentially arrhythmogenic ventricular scars (29).

ECG indicators of RV conduction abnormalities (excluding RBBB) are now classified as minor criteria. These include an ECG pattern in right precordial leads showing a terminal activation duration (TAD) of the QRS $\geq$55 msec from the nadir of the S wave to the end of the QRS. The epsilon wave, characterized by low-amplitude high-frequency signals between the end of the QRS complex and the onset of the T wave in right precordial leads, is also considered a minor criterion. The reason for no longer considering it as a major criterion is due to the demonstrated high interobserver variability, and the influence of ECG filtering and sampling rate in its interpretation. Moreover, the relative impact of the epsilon wave on ACM diagnosis is usually low, as patients are unlikely to express an epsilon wave as an isolated finding and in the vast majority of patients it is accompanied by other clinical manifestations (30).

The presence of low QRS voltages in limb leads (peak-to-peak QRS amplitude $<$0.5 mV) indicates LV involvement. This reduction in electrical activity generation may be due to fibro-fatty replacement of LV myocardial mass. It serves as a major criterion in the absence of other potential causes of low QRS voltages, such as emphysema, obesity, pericardial effusion, or inappropriate setting of low band-pass filters ($<$100 Hz) (31,32).

5. **Arrhythmias**

The evaluation of the arrhythmias has evolved from considering only complex VAs, such as non-sustained or sustained ventricular tachycardia, in the 2010 Task Force criteria, to including premature ventricular beats (PVBs). Premature ventricular beats arising from or near fibro-fatty tissue are typical of ACM. The assessment of PVBs involves considering their absolute count ($>$500 PVBs/24 h), complexity (sustained or non-sustained VT), and morphology on 12-lead ECG, 24-hour Holter monitoring, or a 12-lead ECG exercise test. According to the European TF criteria, PVBs or VT exhibiting a LBBB/superior axis morphology are more specific for ACM as they originate from the RV free wall or interventricular septum, thereby classifying them as a major criterion. Conversely, a LBBB with an inferior axis morphology is regarded as less specific for ACM, since PVBs originating from the RVOT are frequently idiopathic, constituting a minor criterion (33).

The identification of PVBs exhibiting a morphology consistent with RBBB, indicating an origin from the LV, and with high frequency, being exercise-induced, or displaying complexity (excluding the fascicular pattern), is categorized as a minor criterion (34). A RBBB with a wide QRS complex in lead V1, a late precordial transition beyond V3, and a superior axis represents the most prevalent morphology in patients with LV scar affecting the lateral or infero-lateral wall, as observed in ABVC and ALVC (22). Additionally, having a history of cardiac arrest resulting from ventricular fibrillation or VT of unknown morphology is considered a minor criterion for both ventricles involvement.

6. **Family history/genetics**

Acknowledging the variability in ACM manifestation and ventricular involvement within the same family carrying the same gene mutation, the category encompassing family history and molecular genetics is applicable to both RV and LV criteria.

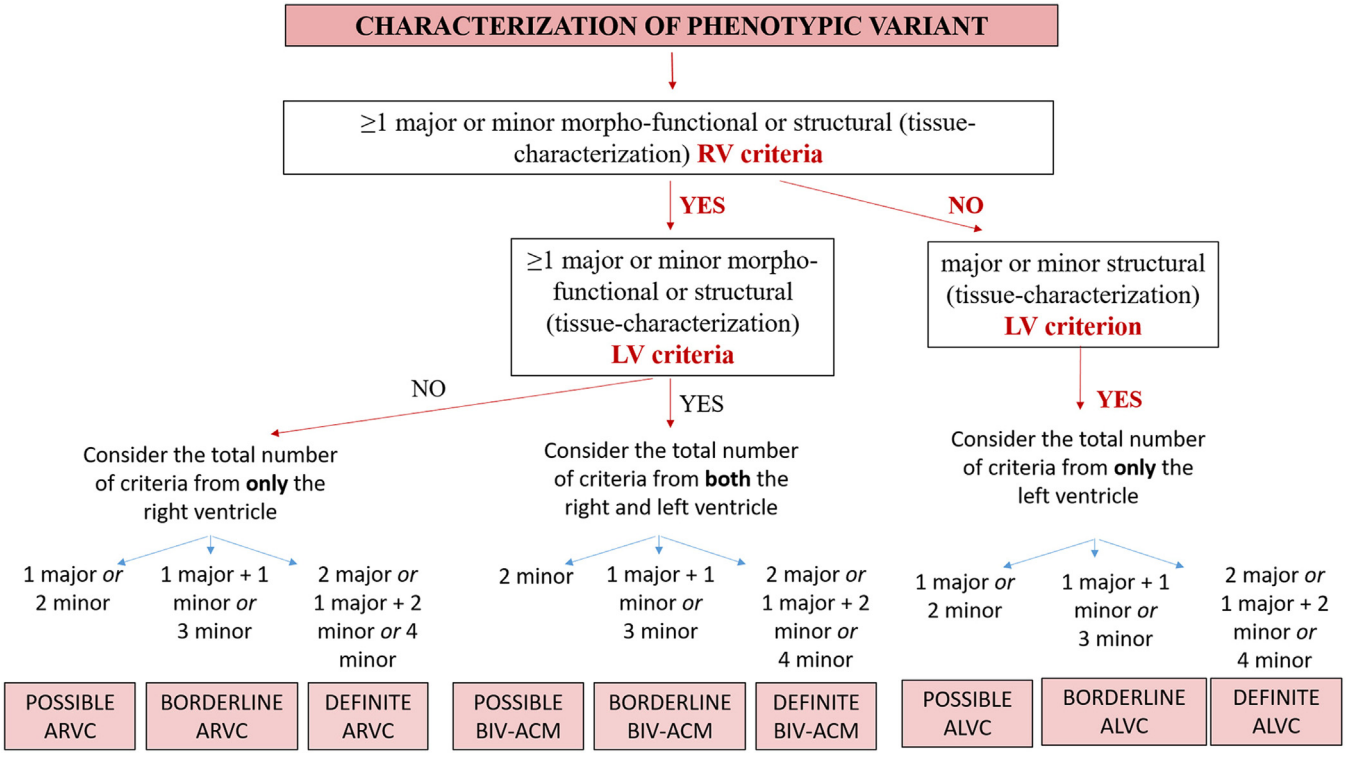

Fig. 1. Flowchart for phenotypic characterization of ACM. From Corrado et al. (12). ALVC, arrhythmogenic left ventricular cardiomyopathy; ARVC, arrhythmogenic right ventricular cardiomyopathy; BIV-ACM, biventricular arrhythmogenic cardiomyopathy; LV, left ventricle; RV, right ventricle.

To prevent misinterpretation of molecular genetic results and misdiagnosis, the criteria provide more specific indications for genotyping (35). Genetic testing is recommended for probands with phenotypic manifestations of ACM, enabling the screening of family members and the identification of gene carriers at a preclinical stage (36). Major criteria consist of finding a pathogenic ACM gene mutation according to the 2015 ACMG classification (37) in the proband and having a first-degree relative with a pathologically confirmed ACM diagnosis or meeting the required criteria for an ACM diagnosis. Minor criteria involve discovering a likely-pathogenic ACM gene mutation in the proband, suspecting ACM without confirmation in a first-degree relative, suspecting ACM in a first-degree relative who experienced sudden death before the age of 35, and confirming an ACM diagnosis in a second-degree relative.

Step 2: Phenotype definition

The second step toward the diagnosis involves pinpointing the specific phenotype of ACM by assessing the fulfillment of criteria related to both RV and LV involvement (Fig. 1). 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 abnormalities) or II (i.e., structural 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. These two categories determine the phenotypic variant: if the criteria are met exclusively for the RV, the diagnosis is ARVC, if they are fulfilled for the LV, it is ALVC. Conversely, if criteria are met for both ventricles, the diagnosis is ABVC. Additionally, the likelihood of disease can be assessed based on the cumulative number of major and minor criteria met for ARVC if only morpho-functional or structural abnormalities of the RV are present, for ALVC when are met just for the LV and ABVC if both ventricles are involved across all categories. A "definite" diagnosis is established if there are either 2 major criteria, or 1 major and 2 minor criteria, or 4 minor criteria fulfilled. A "borderline" diagnosis is assigned if there are either 1 major and 1 minor criterion, or 3 minor criteria met. A "possible" diagnosis is indicated if there is either 1 major criterion or 2 minor criteria satisfied (38).

Step 3: Etiology and classification

ACM is more commonly inherited as an autosomal dominant trait and exhibits variable phenotypic expression and incomplete penetrance. Pathogenic variants in genes encoding desmosomal proteins are the main cause of inherited ACM, making up around 50 % of cases. Desmosomes are critical for the electromechanical connection of cardiomyocytes and intracellular signaling. While classical ACM, with manifestations in both the right and left sides, is primarily associated with desmosomal gene defects, ACM can also stem from non-desmosomal genes (“genocopies”) encoding cytoskeletal components, such as Filamin C or Fosfolamban or may occur as cardiac involvement of inherited neuromuscular disorders (21,36,39). More details about genetics can be found in the Supplementary Materials. 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.

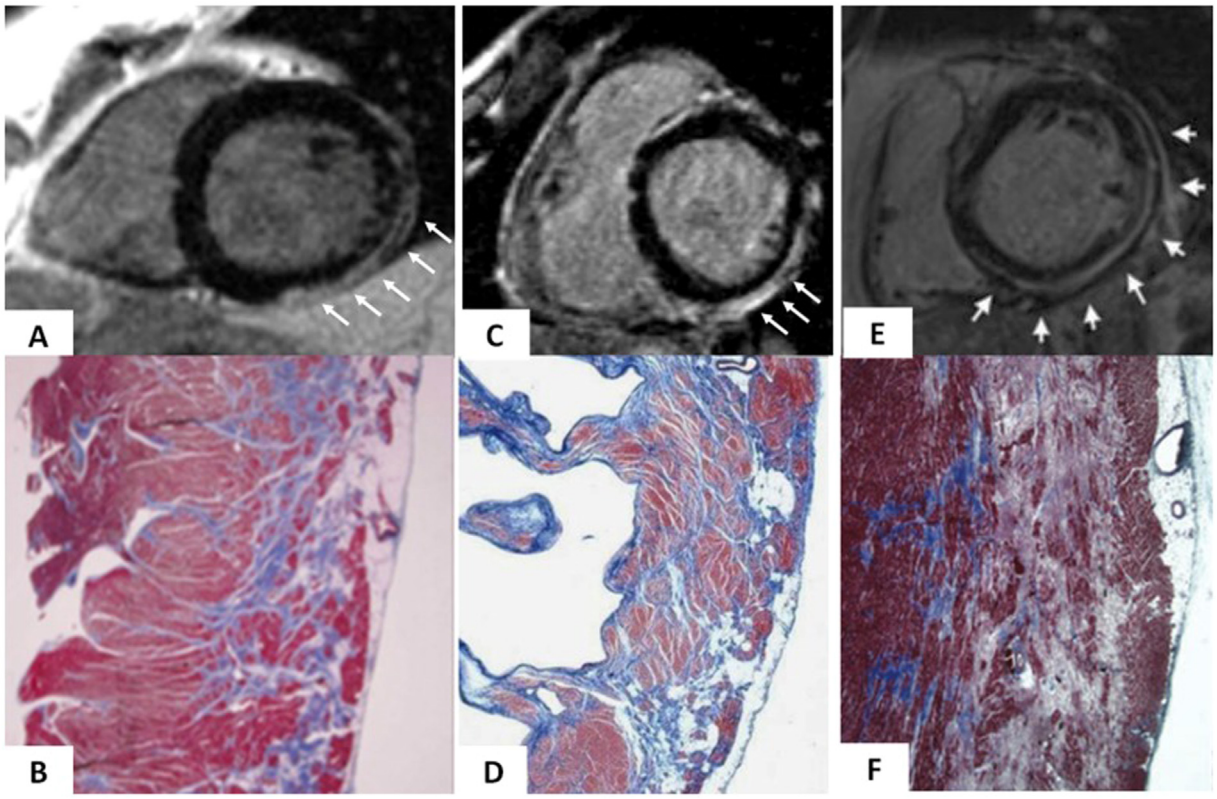

Fig. 2. Cardiac magnetic resonance tissue characterization and histopathologic findings of some ACM phenotypic variants. Muscular dystrophy variant (genocopy): CMR post-contrast T1 inversion recovery (IR) sequences in short-axis view display a subepicardial stria of late gadolinium enhancement (LGE) in the left ventricular wall (arrows) (A). Corresponding histopathologic analysis of the inferolateral left ventricular wall shows replacement-type fibrosis confined to the outer-mid layer of the musculature (B). Post-myocarditis variant (phenocopy): CMR post-contrast T1IR sequences in short-axis view exhibit subepicardial LGE of the inferolateral left ventricular wall (C). The corresponding histopathologic view demonstrates extensive fibro-fatty myocardial replacement in the subepicardial layer (D). Desmosomal gene-related form (prototype disease phenotype): post-contrast T1 inversion recovery (T1IR) sequences in short-axis view show subepicardial late gadolinium enhancement (LGE) of the infero-lateral left ventricular wall in a carrier of the DSP-gene mutation (E). Histopathologic examination reveals fibro-fatty myocardial replacement in the outer layer of the infero-lateral left ventricular wall in a sudden cardiac death victim with a DSP-gene mutation (F). Adapted from (29).

Inflammatory cardiomyopathies, such as post-viral myocarditis, cardiac sarcoidosis, and cardiomyopathies associated with autoimmune multisystem diseases, have the potential to mimic the ACM phenotype (“phenocopies”) and achieve the diagnostic score, Fig. 2. The differentiation between these various etiological categories poses a challenge, and emerging evidence suggests an intricate interaction between genetic factors and myocardial inflammation (40). Importantly, the presence of non-ischemic myocardial scar following an episode of overt acute myocarditis does not exclude a genetic etiology. Indeed, in genetically-determined ACM, myocyte death may be mediated by inflammation with clinical presentation in the form of acute myocarditis-like episodes (so called "hot phases" of the disease) (40).

In the 2020 Padua criteria, the left-dominant form could only be diagnosed with a positive molecular genetic testing always leading to a “definite” disease diagnosis. The 2023 European Task force criteria offered a new perspective of the diagnosis of the left-sided disease variant, which can be achieved even in the absence of a genetic background and classified not only as “definitive” but also as “possible” or “borderline”. Indeed, the European TF etiological classification of ACM encompasses a spectrum of conditions, both genetic and non-genetic, affecting the RV, LV, or both. This classification underscores that the prominent non-ischemic ventricular myocardial scarring associated with VAs is a phenotypic feature common to the various etiologies and accounts for their increased risk of SCD, because myocardial scarring is a distinctive arrhythmic substrate. Identifying the specific cause is crucial for determining clinical outcomes, disease progression, involvement of multiple organ system and the risk of SCD, as these factors vary depending on the etiology. Targeted clinical work-up, based on disease-specific tests and diagnostic findings, is essential to characterize the clinical and prognostic disease profile. Finally, a significant portion of cases may fall under the classification of "idiopathic" ACM, which is diagnosed when patients exhibit a disease phenotype meeting diagnostic criteria, but the etiology remains unknown after thorough clinical and genetic evaluation (12). So, according to the proposed etiologic classification the disease may be genetic (due to an identified disease-causing gene defect) or familial due to an unknown gene defect “gene elusive”, non-genetic due to an identified acquired disease (phenocopy), or idiopathic when the cause of the disease is not identifiable (it may also include non-familial disease due to an unknown gene defect).

Conclusions

This review highlights the limitations of the 2010 TF criteria and emphasizes the need of using updated criteria for diagnosis of ACM. The 2020 Padua criteria and the updated most recent 2023 European TF criteria, aim to improve diagnostic accuracy by contrast-enhanced CMR particularly to identify patients with left-sided disease variants, which were previously underdiagnosed and undertreated. An important novelty is the proposal of the new designation "scarring/arrhythmogenic cardiomyopathy," which emphasizes the diagnostic hallmark of the disease which consists in the myocardial scarring underlying malignant ventricular arrhythmias,

common to the different phenotypic variants and disease etiologies.

Although the clinical utility of the new diagnostic approach to improve the diagnosis of ACM has been validated in the clinical practice by several studies, its further application in larger cohorts of patients is warranted.

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None.

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Francesca Graziano: Writing – review & editing, Writing – original draft, Conceptualization. **Alessandro Zorzi:** Writing – review & editing, Writing – original draft, Conceptualization. **Alberto Cipriani:** Writing – review & editing, Writing – original draft. **Barbara Bauce:** Writing – review & editing, Writing – original draft, Conceptualization. **Ilaria Rigato:** Writing – review & editing, Writing – original draft. **Martina Perazzolo Marra:** Writing – review & editing, Writing – original draft. **Hajnalka Vago:** Writing – review & editing. **Bela Merkely:** Writing – review & editing. **Kalliopi Pilichou:** Writing – review & editing, Writing – original draft. **Cristina Basso:** Writing – review & editing, Writing – original draft. **Domenico Corrado:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tcm.2024.09.002.

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