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Critical analysis of the 2023 ESC guidelines on cardiomyopathy management

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The first European Society of Cardiology (ESC) guidelines on the management of cardiomyopathies (CMPs), published 1 year ago, remain highly relevant. These guidelines provide a comprehensive framework to manage the complexity of CMPs, consolidating previous approaches. All CMPs are now addressed systematically in one document. The ESC recommends a 'CMP-oriented' approach, emphasizing thorough clinical assessments and phenotype-first categorization into hypertrophic, dilated, arrhythmogenic, restrictive, and non-dilated left ventricular CMP. Despite the utility of this method, certain classifications, such as arrhythmogenic right ventricular CMP and the novel non-dilated left ventricular CMP, raise controversies. Key advances in the guidelines include the use of genetic testing and cardiac magnetic resonance imaging to refine diagnoses and inform treatment, especially for high-risk genotypes. These guidelines advocate for personalized, multidisciplinary care. Overall, they represent a significant step forward but highlight the evolving nature of CMP management as scientific understanding progresses.

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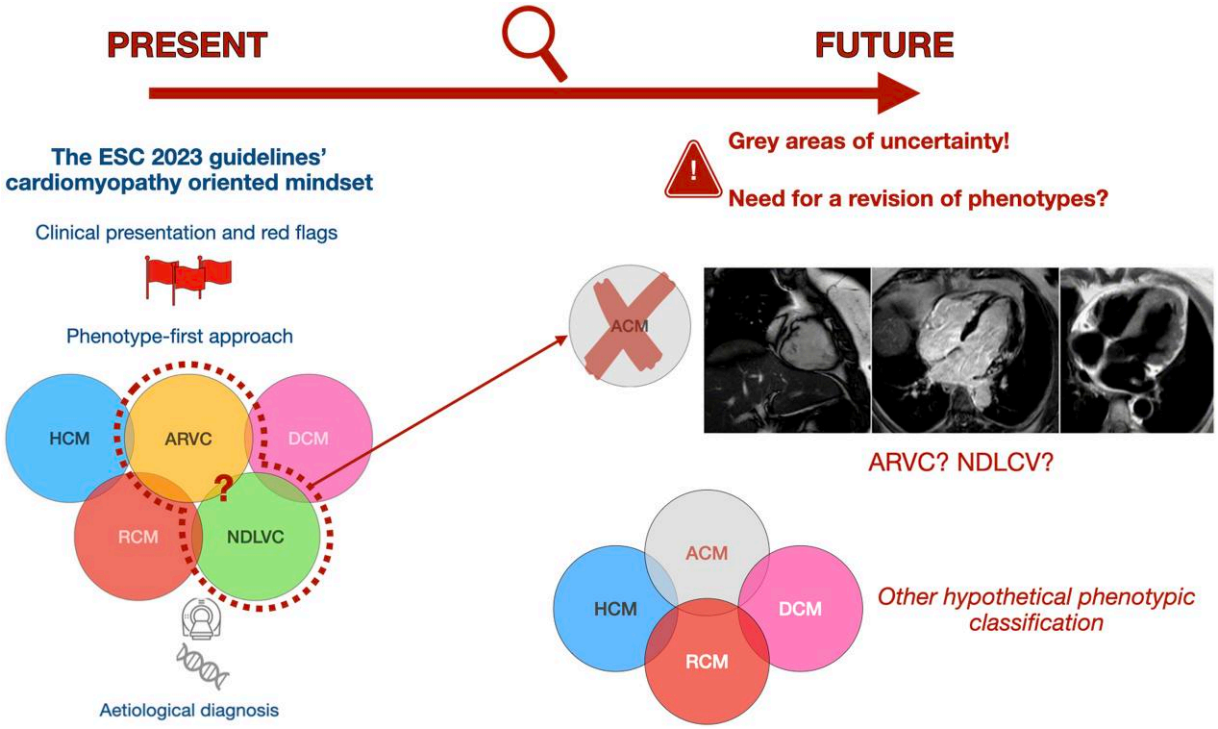
Graphical Abstract On the left, iconographic representation of the workflow presented by the 2023 ESC guidelines on cardiomyopathies, from clinical red flags to phenotype and then the aetiological diagnosis through cardiac magnetic resonance (CMR) and genotype testing. On the right, the controversies on these guidelines' phenotypes are presented through the CMR images of an individual with a *DSP* cardiomyopathy that highlights the overlap and grey zones between arrhythmogenic right ventricular cardiomyopathy and non-dilated left ventricular cardiomyopathy, once filled by arrhythmogenic cardiomyopathy (ACM). An alternative classification with only four phenotypes that include ACM is hypothesized.



One year after their publication, the first European Society of Cardiology (ESC) guidelines on the management of cardiomyopathies (CMPs)[1] are still extremely timely and relevant.

These guidelines have established a much-needed framework for the treatment of CMPs. The document had the merit of putting in order the complex and heterogenous word of CMPs, facing the need that an international scientific society provides healthcare professionals with indications about the challenging management of these cardiac disorders and introducing a document that will serve as a backbone to be further implemented as scientific knowledge evolves. For the first time, all CMPs are addressed in one single document.

Cardiomyopathies are defined as an alteration of the myocardium in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease, hypertension, valvular disease, or congenital heart disease.

The cardiomyopathy mindset

The ESC guidelines advocate for a systematic approach to managing CMPs. This approach begins with a systematic and multifaceted evaluation that includes a thorough clinical evaluation, including a patient's family history, electrocardiogram (ECG) and Holter monitoring, laboratory tests, and multimodality imaging [class of recommendation I, level of evidence (LoE) C]. These findings need to be interpreted to suspect and ultimately formulate an aetiological diagnosis. First and foremost, this step-by-step method starts from the cardiac phenotype, whose importance in identification is well stressed by the guidelines. Patients present with specific cardiac morphological characteristics, and the clinician must examine them with a deductive method. In doing so, the guidelines encourage the systematic use of a 'CMP-oriented' approach, based on red flags that the clinician must look out for. The red-flag approach is particularly well delineated when approaching patients with suspected Anderson–Fabry disease or cardiac amyloidosis. This diagnostic process revolves around the patient presentation in terms of sign and symptoms of heart failure, arrhythmias, abnormal ECG findings, and family history of CMP or sudden cardiac death (SCD). In particular, left (LV) and right ventricles (RV) should be characterized in terms of morphology (wall thickness and volumes) and function (systolic and diastolic), and the myocardium should be analysed as a tissue, whether

scarred, fibrotic, fatty replaced, or infiltrated. This whole pathway should be patient centred and should involve a multidisciplinary team for optimal care (class I, LoE C).

Phenotype-first approach: controversies

One of the core strategies in these guidelines is the phenotype-first approach. Once gathered all the above-mentioned information, the ESC guidelines categorize CMPs into five main phenotypes: hypertrophic CMP (HCM), dilated CMP (DCM), arrhythmogenic right ventricular CMP (ARVC), restrictive CMP (RCM), and the newly introduced non-dilated left ventricular CMP (NDLVC). Each phenotype serves as a starting point for clinicians to further investigate, looking for additional traits that should then be investigated to decline these phenotypes and finally identify its underlying aetiological diagnosis. Among these, there is genetic testing, the final step towards a precise and individualized diagnosis.

However, while this approach certainly deserves credit,[2] there are several controversies about the proposed phenotypes. Specifically, the ARVC and NDLVC phenotypes along with the elimination of arrhythmogenic CMP (ACM) are somewhat puzzling.

Arrhythmogenic cardiomyopathy is characterized by fibro-fatty replacement of the ventricular myocardium, predisposing to ventricular arrhythmias and SCD.[3] Pathogenesis is driven by different gene variants, including but not limited to desmosomal genes.[4] The classical phenotype predominantly involves the RV (hence ARVC). But over time, thanks to the widespread use of cardiac magnetic resonance (CMR), genetic testing, and post-mortem investigations, it has been recognized that the LV is also frequently involved. These variants are characterized by biventricular or even LV-predominant involvement. Recently, due to the low sensitivity of 2010 Task Force Criteria, especially for left-sided variants, a European Task Force proposed new diagnostic criteria for the full spectrum of the disease.[5] However, the comprehensive ACM phenotype has been eliminated by the guidelines.

Instead, ARVC has remained with its >20-year-old diagnostic criteria, which only account for the right ventricular involvement of this disease. This is perhaps the least innovative point of these guidelines. In fact, by doing so, while ARVC with a predominant right ventricular phenotype and some left ventricular involvement remains labelled as 'ARVC', biventricular and left-dominant ventricular phenotypes fall under the NDLVC definition. Furthermore, there is uncertainty regarding the classification of disease variants characterized by symmetrical involvement of the ventricles (i.e. biventricular ACM).

Non-dilated left ventricular cardiomyopathy is defined as the presence of non-ischaemic LV scarring or lipomatous myocardial replacement, in the absence of LV dilatation, with or without systolic dysfunction, or as isolated global LV hypokinaesia without scarring and without ventricular dilatation. According to this definition, NDLVC includes individuals with DCM intermediate phenotypes, such as early-stage DCM, but also genetically determined insidious CMP forms such as those caused by *LMNA* or *DSP* pathogenic variants.[6] To provide two examples and opposed ends of this continuum, it will be labelled as NDLVC the patient with only two segments of LV scar after an uncomplicated myocarditis, with non-remodelled LV and the extensively fibrotic severely hypokinetic and dysfunctional LV of a laminopathy. It is evident that these are two very different settings in terms of prognosis and medical management, and if the classification is not elaborated forward, it could be dangerously misleading. While it is stressed by the authors that phenotypes serve for the initial assessment as a starting point and not for the dynamic disease evolution, this inevitably leads to confusion. Therefore, while the phenotype-first approach is a useful basis, its limitations become evident when dealing with diseases like ARVC and NDLVC. Further refinement and elaboration of these classifications are necessary to avoid confusion and ensure that patients receive an appropriate diagnosis and consequently the most correct level of care.

Key guideline novelties

The guidelines introduce three main novelties significantly impacting the management of CMPs.

First, much attention is paid to genetic testing. In individuals with a diagnosed CMP, it is recommended to confirm the diagnosis, if it informs prognosis, treatment selection, or reproductive management or where it allows cascade genetic screening of their family members (class I, LoE B).[7] Regardless of whether the test is performed, genetic counselling is recommended for all families with a diagnosed or suspected inherited CMP (class I, LoE B). Importantly, the guidelines specify that this counselling is to be performed by an appropriately trained healthcare professional. Starting with first-degree relatives and going down the family tree, cascade genetic testing is to be offered to adult at-risk relatives when a pathogenic (P) or likely pathogenic (LP) variant is detected in the proband (class I, LoE B). When a variant of uncertain significance is detected in the proband, testing its presence in family members should be considered only when this allows variant interpretation through segregation analysis (class IIa, LoE C).

To offer an example of the role genetic testing has in the management of CMPs, certain high-risk genotypes contribute to the indications for device implantation in DCM and NDLVC, such as *FLNC*, *DSP*, *PLN*, *LMNA*, *TMEM43*, and *RMB20*. When an individual affected by DCM/NDLVC carries a P/LP variant in one of these genes that have been associated to SCD,[8-10] an implantable cardioverter defibrillator (ICD) should be considered in primary prevention even with left ventricular ejection fraction (LVEF) > 35% when there are additional risk factors, such as syncope or presence of late gadolinium enhancement (LGE) in CMR (class IIa, LoE C and class IIb, LoE C if absence of risk factors). In spite of the help a positive genotype provides in arrhythmic risk stratification, it shall not be forgotten that 60–70% of DCM cases do not have a genotypic diagnosis.[11] In a

similar way, despite the positive genetic yield is higher in HCM,[12] there is no evidence at present of how genetics can support therapeutic choices; therefore, the guidelines do not include genetic results among the evidence to be used for arrhythmic risk stratification.

A crucial role in the management of CMPs is given to CMR, which appears extensively throughout the document. It is recommended for all patients with a CMP at initial evaluation (class I, LoE B).[13] Cardiac magnetic resonance should also be considered during follow-up of patients with CMP (class IIa, LoE C), ideally every 2–5 years, depending on the extent and severity of the disease detected in the first scan. The guidelines specify that at initial evaluation, CMR should be complete of all sequences: cine imaging, T_2, pre- and post-contrast T_1 mapping, and LGE.

Cardiac magnetic resonance is the key diagnostic test to identify the newly proposed phenotype of NDLVC, where myocardial scarring detected by this imaging technique is enough for the diagnosis. It is worth underlying that CMR should also be considered in the screening of families in which a genetic variant has been associated with a CMP, for the assessment of genotype-positive phenotype-negative individuals (class IIa, LoE B).

As it goes for genetic testing, also CMR has implications not only in the diagnosis and follow-up of CMPs but also in their management, especially in terms of arrhythmic risk stratification. As already stated, LGE presence is an additional risk factor that contributes to primary prevention ICD decision in DCM and NDLVC.[14] In HCM, the presence of extensive LGE (≥15%) may be used to aid decision about prophylactic ICD implantation in those cases in which the HCM-SCD score model yields a low 5-year risk.[15]

Finally, the guidelines contain a praiseworthy section on sport activity recommendations, also considering genotype-positive phenotype-negative individuals, whose management is often challenging. Regular low- to moderate-intensity physical exercise is recommended in all patients with a CMP (class I, LoE C). Concerning high-intensity sports, recommendations are different depending on the CMP phenotype. In HCM, it can be considered in genotype-positive phenotype-negative individuals (class IIa, LoE C) and in individuals with mild left ventricular hypertrophy and absence of left ventricular outflow tract obstruction (class IIb, LoE C), the latter in fact contraindicates high-intensity exercise (class III, LoE C). In ARVC, moderate- to high-intensity activity is not recommended (class III, LoE B), and its avoidance may be considered in genotype-positive phenotype-negative family members (class IIb, LoE C). In DCM and NDLVC, except for individuals bearing *LMNA* or *TMEM43* variants, moderate- to high-intensity physical exercise can be performed in gene-positive individuals with negative phenotype (class IIa, LoE C); this recommendation may reasonably be extended to all arrhythmic genotypes. Furthermore, it may be considered in asymptomatic and optimally treated individuals with an LVEF >40%, provided exercise-induced complex arrhythmias have been excluded (class IIb, LoE B).

Conclusions and future perspectives

An attentive reader will have already noticed that while these guidelines provide a structured framework, the vast majority of the recommendations they offer have low levels of evidence. Unfortunately, due to the low prevalence and complexity of these cardiac disorders, expert recommendations often need to rely solely on observational data and expert consensus. At times, this makes these guidelines more open to interpretation. It should be stressed once again how the management of these disorders should be solidly rooted on clinical practice, multidisciplinary evaluation, shared decision-making, and a global approach to the patient. On the other hand, this calls for further research and collaborative efforts to characterize, understand, and treat these complex disorders.

Finally, it should always be remembered that classifications help to fill in the gaps in knowledge, and they should always be re-evaluated and updated as knowledge evolves.

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Data availability

No new data were generated or analysed in support of this research.

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