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Dilated Cardiomyopathy: Current Mechanisms and Clinical Approach: A Narrative Review

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ABSTRATC/SUMMARY

Dilated Cardiomyopathy (DCM) is defined as a condition in which the patient presents with left ventricular dilatation (in adults, an Left Ventricular (LV) end-diastolic diameter >58 mm in males and >52 mm in females, and an LV end-diastolic volume index ≥75 mL/m2 in males and ≥62 mL/m2 in females, as determined by echocardiogram [1,2] accompanied by significant compromise in ejection fraction (LVEF <50%). This condition should not be attributed to abnormal loading conditions (e.g., hypertension, valvular disease) or significant coronary artery disease (significant stenosis of the left main coronary artery or proximal third of the anterior descending artery, or significant stenosis in 2 or more of the other epicardial vessels) [3,4].

DCM is actually a non-specific phenotype that's produced as a final result of multiple genetic and environmental interactions. This means that it's a clinical entity that can be produced by multiple etiologies [5]. At first, it can be classified as "Familial/Genetic" and "Non-Familial" depending on whether it follows a pattern of inheritance. It's estimated that at least 25% of patients in the West who present the disease would have evidence of a familial disease, with a pattern of inheritance that is generally autosomal dominant [6].

This condition may be considered ‘Familial’ when 2 or more first or second degree relatives express the disease phenotype, or when a first degree relative presents with an autopsy compatible with dilated cardiomyopathy following sudden death before the age of 50 years [7].

A working group of the European Society of Cardiology recently proposed a clinical spectrum of presentation that expands the classic definition [8]. This new definition initially recognizes a preclinical phase of the disease that includes asymptomatic relatives of index cases with expression of diseaserelated genes, patients with isolated ventricular dilatation without systolic dysfunction, and patients with neither dilatation nor systolic dysfunction, but who manifest arrhythmias or conduction disturbances. Subsequently, it is recognized that patients may progress into two groups: one that presents the classic disease with dilatation and ventricular dysfunction, and another that presents a hypokinetic ventricle (LVEF below 45%) but without dilatation. The

disease is then recognized as a spectrum in which the phenotype progressively evolves. This group of patients with a non-dilated hypokinetic heart represents approximately one-third of the patients in the clinical phase of the DCM universe [8].

EPIDEMIOLOGY

There is a paucity of consistent data regarding the epidemiology of DCM. The earliest data originate from US studies conducted in Olmstead County between 1975 and 1984 [9]. This study estimated an approximate prevalence of 1 in 2700 individuals carrying the disease. However, the study was limited by the fact that at that time echocardiography was an emerging technology and many carrier patients may never have been diagnosed [9]. This study also indicated that the ratio of patients with DCM to those with hypertrophic cardiomyopathy is significantly higher, with a ratio approaching 2:1. However, subsequent studies have estimated the prevalence of hypertrophic cardiomyopathy to be approximately ten times higher than that observed in the Olmstead County study [10]. This 10-fold difference has led to questions about the current prevalence of DCM. In a family-based, cross-sectional study of 1220 patients with DCM and their 1693 family members, the estimated familial DCM prevalence was 29.7% and the estimated DCM risk by age 80 years in family members was 19% [11]. In a recent study the annual number of hospitalizations for DCM in USA increased from 31,078 to 43,585 between 2016 to 2020 [12]. The commonest age groups involved were 65 to 74 years (23.82%) followed by 55 to 64 years (23.08%). When stratified by race, white males were hospitalized more frequently than white females, whereas more black females were hospitalized compared to their male counterparts [12].

A formal epidemiological study is needed to truly determine the prevalence and incidence of DCM, including the universe of patients with an asymptomatic phenotype. However, even considering the limitations of the figures, DCM is still commonly present in the universe of patients with heart failure, constituting one of the most frequent etiologies in transplant recipients. In a registry of heart transplant recipients from the University of Padua between 1985 and 2016, DCM accounted for 39% of patients who underwent transplantation [13]. Similarly, in a national registry, DCM accounted for 80% of pediatric transplanted patients [14].

ETIOLOGIES

DCM can be the end product of multiple etiologies, which may correspond to diseases with specific treatments. However, the most common etiology of DCM is idiopathic and without an identifiable cause [15]. Therefore, an appropriate etiological study becomes central to the study of DCM, as it has therapeutic and prognostic implications. The possible etiologies are multiple and consist of several groups, be they genetic, inflammatory/infectious causes, tachycardia-induced cardio-myopathies, toxins, among others [5] (Table 1).

Genetics/Familial: Approximately 25-40% of DCM and 10-20% of sporadic or acquired dilated cardiomyopathy have an identifiable monogenic cause [16]. Studies in families have established that 20-40% of patients with DCM may be classified as having a familial etiology if first-degree relatives of the index case are screened, usually with echocardiography [17,18]. Most of them are autosomal dominant.

Such studies have served as a basis for identifying the multiple genes involved in the etiology of the pathology (Table 2).

Mutations in multiple genes have now been identified as the cause of DCM. The most frequently identified mutation is in the TTN gene [16], which encodes the titin protein, a structural element of the sarcomere. This mutation is present in 25% of familial cases and 18% of sporadic cases [19]. TTN variants are present in approximately 0.5% of the general population, many of whom will not develop dilated cardiomyopathy without a second environmental or genetic trigger [16].

The second most frequently altered gene is LMNA (6% of cases), which encodes Laminin A/C in the nuclear membrane. This is a relevant diagnostic factor as it can be associated with a phenotype of DCM presentation with first-degree AV block or ventricular arrhythmias [8].

Further gene mutations have been identified, including those affecting the myocyte. These include MYH7 (4% of cases), TNNT2 (3%), MYBPC3 (2%), RBM20 (2%), MYPN (3-4%), SCN5A (2-3%), and several others.

Some cases have mutations in X-associated genes. These mutations express the DCM phenotype, and may be associated with neuromuscular pathologies or specific clinical syndromes [8].

In the most recent comprehensive clinical cardiomyopathy guidelines one of the main innovations lies in the value of genetics and tissue characterization byCardiac Magnetic Resonance (CMR) in risk stratification of sudden cardiac death, as previously introduced in the 2022 guidelines for ventricular arrhythmias [1,2]. Besides, both the DSP and TMEM43 genes are added as high-risk genotypes to those previously described (FLNC, RBM20, LMNA, PLN) [1,2] Table 2. These guidelines also specify the situations requiring consideration of an Implantable Cardioverter-Defibrillator (ICD) with LVEF > 35%. The use of a risk calculator for LMNA variant is also recommended, disregarding classic clinical criteria. The document also suggests that ICD implantation may be considered in cases with a negative genetic study when NonSustained Ventricular Tachycardia (NSVT), family history of sudden cardiac death, or extensive Late Gadolinium Enhancement (LGE) are present [1,2].

It is important to note that, as with multiple genes causing the DCM phenotype, some of these genes are related to the expression of other cardiomyopathies. Mutations in TTN can also be expressed in patients with hypertrophic cardiomyopathy, mutations in LMNA can be seen in patients with neuromuscular diseases, and mutations in the SCN5A gene can be observed in patients with channelopathies. Mutations in the PKP2 gene can be associated with both DCM and arrhythmogenic dysplasia. The relationship between gene mutations and phenotype expression is complex. For example, a patient with DCM related to TTN mutations could have a first-degree relative with alterations in the same gene expressing another pathological phenotype. It would be debatable whether to consider this as a familial disease or whether it is a question of two different pathologies [17].

High-risk genotypes (Table 2) and associated predictors of sudden cardiac death [1] are the LMNA gene (annual SCD rate 5-10%), FLNC-truncating variants (annual SCD rate 5-10%, high risk in the presence of LGE on CMR and LVEF < 45%), TMEM43 (annual SCD rate 5-10%; high risk in males and in females with LVEF <45% or non sustained VT or LGE on CMR or >200 ventricular ectopic beats on 24h Holter monitoring), PLN (annual SCD rate 3-5%; high risk in the presence of LVEF < 45%, LGE on CMR, non sustained VT) and RBM20 and DSP (both with annual SCD rate 3-5% as well as high risk in the presence of LVEF < 45%, LGE on CMR).

Inflammatory/Infeccious: The concept of inflammatory cardiomyopathy (defined as myocarditis associated with ventricular dysfunction) includes subtypes of inflammatory, infectious, toxic secondary and idiopathic

causes [20]. Biopsy-proven myocarditis may be present in 9-16% of DCM cases, and in turn, 30% of biopsy-proven myocarditis cases may progress to DCM [21-24].

This cardiomyopathy may be caused by a multitude of entities. In developed countries, the most prevalent cause is lymphocytic myocarditis, which is of viral etiology. However, infectious causes secondary to bacteria, parasites, or fungi, autoimmune causes associated with connective tissue disease (e.g., lupus, scleroderma, polymyositis, dermatomyositis), giant cell myocarditis, sarcoidosis, hypereosinophilic conditions, and exposure to toxins such as cocaine, arsenic, scorpion venom, and others have been described [25]. Regarding viral etiologies, it should be noted that viral prevalence varies in different studies depending on time and location. For instance, a study in Germany describes a higher predominance of positivity for Parvovirus B19 identified by PCR in biopsies [23]. Another study contemporary to the previous one, but in the United States, describes a predominance of Adenovirus and Enterovirus [24]. The infectious/inflammatory process causes myocardial necrosis, exposing autoantigens that can be presented to the immune system. It appears that progression from myocarditis to dilated cardiomyopathy occurs in patients with persistent inflammation who cannot clear the infectious insult (chronic infection) or who have developed autoantibodies directed against myocardial proteins, initiating a chronic autoimmune process. It is likely that a certain degree of genetic predisposition is required for either of these to occur [21].

Toxicity: Exposure to certain substances may eventually produce the phenotype of ventricular dysfunction with a dilated heart. Examples of this are prolonged consumption of alcohol, cocaine, and exposure to chemotherapeutic drugs such as anthracyclines. It has been documented that consuming the equivalent of more than 80 grams of alcohol daily for 5 years generates the risk of producing alcoholic cardiomyopathy [25]. Long-term use of cocaine has also been linked to the development of dilated cardiomyopathy and malignant arrhythmias [26]. Anthracycline therapy (particularly doxorubicin, epirubicin, and idarubicin) has a dose-dependent association with the development of ventricular dysfunction, which is associated with high mortality rates [27].

Other causes: Other conditions have also been related to the development of DCM, among which stand out conduction disturbances (right ventricular pacing, complete left bundle branch block, pre-excitation) [28], arrhythmia-induced cardiomyopathy (suspected in patients with a basal heart rate higher than 100 bpm, in patients with atrial fibrillation and in patients with frequent ventricular extrasystoles with a load higher than 10% of the beats of the day) [29], those related to pregnancy, endocrine or metabolic etiologies, among others [5].

PATHOPHYSIOLOGY

The characteristic pathophysiologic feature of DCM is systolic dysfunction of the left or both ventricles. It is thought that reduced sarcomere contractility increases ventricular volumes to maintain cardiac output through the Frank-Starling mechanism [30], which may result in the thin-walled dilated LV appearance that is observed in overt DCM. It is also believed that Frank and Starling demonstrated that increased ventricular preload augments contractility, but excessive pressure and volume induces a plateau and then a reduction in myocardial contraction [30]. Abnormal hemodynamics may lead to further Left Ventricular (LV) remodeling. Cardiac remodeling in response to an inciting myocardial insult or an underlying genetic abnormality may be considered

the pathognomonic aspect of DCM [30]. Progressive dilatation of the ventricles results in significant tricuspid and mitral valve regurgitation, which further reduces the ejection fraction and increases the ventricular wall stress and end-systolic volumes [15]. Early compensatory mechanisms include an increase in heart rate and the tone of the peripheral vascular system. However, these compensatory mechanisms lead to geometric remodeling of the ventricles leading to worsening of the myocardial injury [15]. In parallel, there is neurohormonal activation of the renin-angiotensin-aldosterone system and an increase in circulating levels of catecholamines. Furthermore, levels of natriuretic peptides are also increased. Ultimately, these compensatory mechanisms become overwhelmed, resulting in heart failure [15].

A pathological examination of myocardial biopsy samples or autopsies of patients with DCM frequently uncovers evidence of an inflammatory cell infiltrate and gene expression patterns compatible with immune cell activation [31]. Immune cells that contribute to remodeling include mast cells, M2 or activated macrophages, and myeloid-derived suppressor cells, T helper 2 (TH2) and TH17 cells [30]. In the case of autoimmune etiologies, B cells that produce autoantibodies that form immune complexes with self-antigens and complement components also play a role. Immune cells release several cytokines that promote remodelling, collagen deposition and fibrosis [31]. Fibrosis is a consequence of inflammation at the site of tissue damage and is the characteristic pathological feature of DCM aside from dilatation [31]. As time progresses, fibrotic scar tissue gradually replaces the damaged tissue, thereby increasing the stiffness of the heart and further accelerating the progression to dilation and heart failure [31].

CLINICAL PRESENTATION AND DIAGNOSTIC EVALUATION

The clinical presentation of DCM can vary considerably. Patients with DCM may require medical attention for the following reasons: symptoms onset (HF or arrhythmia related), incidental abnormal findings, or as a result of family screening following the diagnosis in a relative [1]. The age of presentation is typically between 20 and 50 years old [32]. Some patients present with exertional dyspnea and edema of the lower extremities, while others present with arrhythmias as their initial symptom. Some patients may also present with cardiogenic shock. Presentation is not typically related to etiology. The symptoms and signs of DCM are mainly related to the degree of ventricular (or biventricular) dysfunction. The symptoms may manifest acutely, subacutely, or chronically [31].

The initial aim of the diagnostic work-up is to confirm the diagnosis of DCM, rule out other possible exclusions (hypertension, coronary artery disease, valvular heart disease), identify the underlying etiology and finally to assess severity and risk stratification. Several diagnostic tools are available for this purpose.

General Laboratory: Biochemical evaluation is an essential part of the etiological evaluation. Troponins, serology for HIV, Chagas and hepatotropic viruses, and a blood count with ESR and C-reactive protein help to rule out inflammatory cardiomyopathy. A blood count with ESR and C-reactive protein also support the inflammatory etiology. The CBC also helps to rule out hypereosinophilia. Autoimmune serology helps to rule out associated inflammatory pathology. The ferritin and ferritin saturation levels are indicative of infiltrative pathology and may have a therapeutic role in detecting iron deficiency. It is essential to consider endocrine and metabolic pathology with thyroid hormone levels, serum creatinine, plasma electrolytes, calcium, glycemia and

other endocrine tests, oriented according to clinical suspicion. Creatine phosphokinase levels, muscle biopsy and electromyography help in the study of a clinically possible associated neuromuscular disease [5].

The electrocardiogram (ECG) remains a crucial diagnostic tool in the initial evaluation of patients with Dilated Cardiomyopathy (DCM). It can provide valuable diagnostic landmarks in risk stratification and, in some cases, serve as an etiological guide. In DCM, the ECG will be abnormal in at least 80% of cases, with findings suggestive of left ventricular hypertrophy (17-69%), LBBB (23-28%), pathological Q waves (26-36%), first-degree AV block (10-23%) and atrial fibrillation (3-25%) [33]. Specific findings, such as first-degree AV block in the context of DCM, may provide valuable insights for the etiological study. This is due to its relationship with sarcoidosis or certain genes involved in the etiology of the disease, such as LMNA or SCN5A. In addition to providing insight into the etiology in question, the LBBB finding guides therapy by suggesting the potential use of Cardiac Resynchronization Therapy (CRT) as part of the therapeutic work-up[33].

Echocardiography:2D and Doppler echocardiogram continue to be fundamental for the diagnostic study of DCM. It has the capacity to measure contractility, evaluate left ventricular and other cardiac chamber dilatation, assess valvular functional status and evaluate dyssynchrony[5]. Given its diagnostic utility, cost-effectiveness, availability and portability, every patient with symptoms of heart failure or suspected heart failure should have an echocardiogram at the onset of the disease and during follow-up [34].

Complementing ultrasound with techniques such as speckle-tracking helps to increase the sensitivity of the examination. The measurement of the longitudinal strain can help to identify the presence of an inflammatory infiltrate and provide diagnostic guidance [31].

Coronary Imaging: Classically, ischemic cardiomyopathy is differentiated from DCM by the presence of significant stenosis of the left main coronary artery or in the proximal third of the anterior descending artery, or significant stenosis in 2 or more of the other epicardial vessels [4]. Coronary anatomy studies should be considered during the diagnostic evaluation of DCM to rule out ischemic cardiomyopathy. Coronary CT angiography or direct coronary angiography are options for this purpose.

Magnetic Resonance Imaging: Cardio resonance has become an increasingly accessible resource in clinical practice. It is outstanding in its ability to perform a better morphological and functional evaluation of cardiac structures than other techniques. It can also perform a characterization of myocardial tissue through the detection of edema and myocardial fibrosis [31].

The detection of edema has a role in the etiological study since its presence is characteristic in certain diseases (e.g. myocarditis, sarcoidosis) [5].

The detection of fibrosis is performed through late gadolinium uptake and has a role in the etiological and prognostic study. Certain patterns of gadolinium uptake are indicative of different etiologies (e.g. muscular dystrophy, previous myocarditis, Chagas disease, coronary artery disease) [5]. The presence of myocardial fibrosis detected in MRI represents a substrate to generate malignant arrhythmias and is associated with a greater number of appropriate discharges in patients with an implantable defibrillator [35]. It is also associated with an increased risk of mortality and cardiovascular morbidity [36]. In turn, the magnitude of fibrosis present is related to the lack of response to medical therapy [37] and to the response to cardiac resynchronization therapy [38].

Current guidelines recommend magnetic resonance imaging as part of the initial evaluation of all cardiomyopathy, assisting in the etiological study, risk stratification and follow-up to monitor disease progression [1].

Endomyocardial biopsy is the gold standard for identifying myocardial inflammation. It requires the collection of multiple samples to perform an appropriate study. The samples taken are used for histological, immunohistochemical and molecular studies with rtPCR for the identification of possible pathogens. It can be used to confirm autoimmune etiologies, such as in patients with heart failure in giant cell myocarditis, eosinophilic myocarditis, vasculitis or cardiac sarcoidosis. The use of this endomyocardial biopsy requires a careful risk *vs*. benefit evaluation and should be reserved mainly for situations where the results generate a change in therapeutic behaviour. It is recommended to be performed under specific scenarios, each with different degrees of recommendation. The strongest recommendations suggest performing it in case of: 1) Heart failure of recent onset (less than two weeks) with hemodynamic compromise and 2) heart failure of recent diagnosis (between two weeks and three months) with left ventricular dilatation and ventricular arrhythmias, second or third degree AV block or refractoriness to medical treatment within one to two weeks [39]. Lower-level recommendations also suggest that a biopsy should be performed in the presence of heart failure associated with eosinophilia, suspected anthracycline-induced heart failure, or in the presence of ventricular arrhythmias that cannot be explained by the clinical context [39].

Some series have reported complications in 6% of cases, of which 2.7% correspond to puncture site complications and 3.3% to myocardial puncture. Among these complications, arrhythmias, conduction abnormalities and perforations may occur [40].

Familial and Genetic Study: In recent cohorts, causative gene variants have been identified in up to 40% of DCM patients and in 10-15% in patients with DCM induced by chemotherapy, alcohol consumption, or pregnancy [1]. The identification of relatives affected by the phenotype of the disease is the most important element orienting a genetic etiology. That is why all patients should have a family history covering at least 3 generations [5].

In the absence of conclusive genetic information in a family, current criteria to consider DCM as familial are [1]: one or more first or second-degree relatives have DCM or when an otherwise unexplained SCD has occurred in a first-degree relative at any age with an established diagnosis of DCM.

In the clinical evaluation of first-degree relatives of the index case where a familial etiology is suspected, screening with clinical assessment, ECG and echocardiogram is recommended. In some cases a Magnetic Resonance Imaging may be considered. This study should be repeated every 5 years in case of negative findings (7). In case a genetic mutation is identified as the cause of DCM in the index case, a genetic study directed to relatives can also be considered. Those relatives who are not carriers of the gene found in the index case could have a more limited follow-up [1].

The finding of the variant of a causal gene in patients with DCM allows a better prediction of the evolution of the disease. It could also contribute to the indication of defibrillator implantation and may guide the screening of family members [1]. The performance of a genetic study in patients with DCM of familial etiology is specifically recommended in the European Society Guidelines 2022 on Sudden Cardiac Death and Ventricular Tachycardia and in the European Guidelines for the Management of Cardiomyopathies [1,41], because the

detection of alterations in certain genes (LMNA, PLN, FLNC, RBM20) could be involved in the decision to implant a defibrillator [1,41].

TREATMENT

Pharmacological treatment: The pharmacological treatment for DCM is largely similar to that indicated for heart failure with reduced ejection fraction. In some cases, it is necessary to add the corresponding therapy for the treatment of specific pathologies (e.g. immunosuppression in inflammatory etiologies) [5]. Prognosis and response to therapy may vary according to the etiology of the disease. For example, idiopathic DCM tends to have a better prognosis than anthracycline-induced DCM [42].

One of the most important factors in determining prognosis is the extent of adverse remodeling. This encompasses the degree of ventricular dilatation, wall thinning, the level of contractility reduction, the presence of functional mitral regurgitation, the extent of myocardial fibrosis, the presence of ventricular dyssynchrony and the enlargement of other chambers of the left ventricle. The objective of therapy is to achieve a reversal of this remodeling (reverse remodeling) [5].

Studies have shown that medical therapy may be associated with reverse remodeling in one third of patients, with a better prognosis in terms of survival or need for transplantation in this group [43]. One factor associated with the development of reverse remodeling was the absence of left bundle branch block. Other predictors of reverse remodeling are disease duration and functional capacity [43] as well as late gadolinium enhacement[1].

Prevention of sudden death-Implantable Cardioverter Defibrillator Indication: Despite the availability of effective treatments, the risk of sudden arrhythmic death in patients with DCM remains a significant challenge in current clinical practice. As a preventive therapy, the use of an Implantable Cardioverter Defibrillator (ICD) is a viable option, offering an effective therapy in preventing deaths from ventricular arrhythmias. However, implantation of a defibrillator is not without complications, particularly in young patients who will require multiple generator changes throughout their lives [1].

The efficacy of the ICD as a secondary prevention therapy in patients who have survived a lethal arrhythmic event or a documented ventricular arrhythmia with hemodynamic deterioration is well established. Studies examining this aspect include AVID, CIDS and CASH, which involved patients with and without coronary etiology who have survived an arrhythmic event. A meta-analysis of these studies indicates that ICD implantation is associated with a 27% relative risk reduction in mortality compared to amiodarone alone. This translates to an annual mortality reduction from 12.3% to 8.8%, suggesting an NNT of 29 [44]. The risk reduction effect is more pronounced when mortality due to arrhythmias is considered (HR 0.5). It is worth noting that the subgroup of patients with the greatest benefit was that of patients with an ejection fraction below 35%.

Available RCTs examining the usefulness of ICDs to prevent SCD and improve survival have included only patients with LVEF ≤35%, with conflicting results [1]. On the other hand, the usefulness of ICD implantation as a primary prevention therapy becomes more debatable. Currently, the main parameter used to predict sudden death events and the decision to implant an ICD is ejection fraction and symptoms of heart failure. An ICD should be considered to reduce the risk of sudden death and allcause mortality in patients with DCM,

symptomatic heart failure, and LVEF ≤35% despite >3 months of optimal medical therapy (IIa recommendation) [1]. Additionally, an ICD should be considered in patients with DCM with a genotype associated with high SCD risk (Table 2) and LVEF >35% in the presence of additional risk factors (such as LGE on CMR, gender and specific estimated 5-year risk of life-threatening arrhythmia) (IIa recommendation) [1].

The largest and most recent randomized study to evaluate the effectiveness of ICD implantation as primary prevention in patients with symptomatic heart failure and an ejection fraction below 35% of non-ischaemic aetiology was the DANISH study [45]. This study did not demonstrate that ICD therapy *vs* medical therapy significantly reduced the outcome of all-cause mortality. The mortality rate in the ICD group was 21.6%, while in the medical therapy group it was 23.4%. The study demonstrated a reduction in sudden death events (4.3% *vs* 8.2%, p=0.005), although it did not achieve a significant difference in allcause mortality (23.4% in the medical therapy group, p=0.28) [45]. The difference between the two groups was statistically significant (p=0.005). The average follow-up period was 5-6 years [45]. This prompts the question of whether the current indication for ICD implantation in all patients with symptoms of heart failure and reduced LVEF is appropriate, despite an proper period of optimal medical therapy. However, subgroup analysis in the DANISH study suggests that there is a mortality benefit in the group of patients younger than 59 years of age. A DANISH post hoc analysis concluded that the age cutoff for benefit in all-cause mortality was 70 years. Patients younger than the aforementioned cutoff exhibited a significant reduction in all-cause mortality (HR 0.70; 95% CI, 0.510.96; p=0.03) in comparison to those aged 70 years and older, where the benefit was not observed [46]. This discrepancy can be attributed, in part, to the higher incidence of deaths unrelated to sudden death events.

In addition to the aforementioned considerations, it is also worth mentioning the results of studies conducted prior to the DANISH trial. A meta-analysis was conducted which included six relevant studies that enrolled patients with ventricular dysfunction of non-ischaemic aetiology. The effectiveness of ICD implantation in primary prevention was evaluated in these studies (CAT, AMIOVIRT, DEFINITE, SCD-HeFT, Pro-ICD and DANISH). The results of this meta-analysis indicated a 22% reduction in all-cause mortality (absolute risk reduction of 4.7%), a 23% reduction in cardiovascular mortality (absolute risk reduction of 3.3%) and a 65% reduction in sudden death events (absolute risk reduction of 4.1%) [47]. One potential limitation of the analysis is the inclusion of studies conducted over 15 years ago, during which time contemporary optimal medical therapy may not have been available. In such a context, the benefits of an ICD may be more pronounced.

It is now understood that ejection fraction as a risk stratification parameter for sudden death has limited performance. In light of this, other factors are being considered that should be taken into account in the decision to install an ICD. One of these is genotype. A recent retrospective study demonstrated that patients diagnosed with DCM and identified as having a disease-causing gene had a worse prognosis than those where screening did not identify any gene [41]. The study found that the HR for malignant arrhythmias was 1.50 with a 95% CI of 0.59-0.99 (P=0.047). The latest European cardiomyopathy guidelines [1] highlight the importance of identifying the highest risk genes, including LMNA, TMEM43, PLN, DSP, RBM20 and variants in the FLNC gene [1].

Another factor that is beginning to be considered in guidelines is the presence and extent of myocardial scarring as determined by late gadolinium uptake on MRI. In a recent retrospective study, late gadolinium uptake was found to be an independent and powerful predictor for arrhythmic endpoints, independent of ejection fraction. This reclassified arrhythmic risk in 34% of patients. Patients with LVEF between 21-35% without late uptake would have a lower risk profile than those with LVEF over 35% but with extensive gadolinium uptake.

The presence of high-risk genes, the extent of gadolinium uptake on cardiac MRI, together with the presence of other risk factors (nonsustained VT, extrasystolic load, among others) are now among the recommendations for consideration of ICD implantation in the latest European Society guidelines [1]. It is worth mentioning that, in view of the above, the indication for ICD implantation as a primary prevention tool in DCM is not a simple decision and should take into account several factors. Finally, the decision to implant must be individualized for each patient.

The 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death have suggested a higher threshold of 10% risk at 5 years to guide primary prevention ICD implantation in patients with DCM and LMNA variants. In this regard, the 2023 European Task Force for Management of cardiomyopathies recommends shared decision-making based on real-world data as well as individual preferences, beliefs, circumstances, and values [1]

Specific Therapies: As previously mentioned, DCM may correspond to the final phenotype of multiple etiologies. Therefore, there is the option that some of them have specific treatment. An example of this is DCM induced by conduction disorders (right ventricular pacing or complete left bundle branch block) that can be treated with the implantation of a resynchronizer [28].

Other examples of specific therapies with variable effectiveness include immunosuppressive therapy in patients with chronic inflammatory cardiomyopathy (more than six months) with histological evidence of lymphocytic myocarditis and absence of virus proven by PCR or the use of interferon beta as antiviral therapy in patients with biopsy-proven myocardial viral infection.

In addition to the aforementioned examples, there are numerous other therapies currently in development or under study with the aim of treating the underlying cause of the disease. This emphasizes the importance of conducting a comprehensive diagnostic work-up.

Table 1: Causes of Dilated Cardiomyopathy.

ETIOLOGIES	
Idiopathic	
Genetic	Details in Table 2
Toxic and overload	Alcohol (ethanol), cocaine, amphetamines, ecstasy, cobalt, anabolic/androgenic steroids, haemochromatosis and other causes of iron overload
Infeccious (after myocarditis)	- Viral: Adenovirus, coxsackie A and B, cytomegalovirus, Epstein-Barr, herpesvirus 6, HIV, parvovirus B19, varicella (chickenpox) - Bacterial:

	Brucellosis, diphtheria, psittacosis, typhoid fever, streptococcus, staphylococcus- - Protozoa: Chagas, toxoplasmosis, malaria - Helminths: Echinococcus, schistosoma, toxocara - Fungal: Aspergillus, candida, cryptococcus, actinomyces
Drugs	Antineoplastic (anthracyclines, antimetabolites, alkylating agents; Taxol; hypomethylating agent, monoclonal antibodies, tyrosine kinase inhibitors; immunomodulating agents) Psychiatric drugs (clozapine, olanzapine, chlorpromazine, risperidone, lithium, methylphenidate, tricyclic antidepressants) Other drugs (all-trans retinoic acid, antiretroviral agents, phenothiazines)
Inflammatory/Infiltrative/ Autoimmune	Systemic lupus erythematosus, rheumatoid arthritis, scleroderma, polymyositis, dermatomyositis, sarcoidosis, Kawasaki, hypersensitivity myocarditis, hypereosinophilia
Neuromuscular Diseases	Muscular Dystrophies (Duchene/Becker/Steinert), Friedreich's Ataxia, Myotonic Dystrophy
Metabolic/Endocrine	Cushing's disease, hypothyroidism, hyperthyroidism, pheochromocytoma, chronic hypocalcemia, hypophosphemia
Nutritional deficiency	Selenium , Thiamine (Beri-Beri), Zinc and copper, Carnitine
Peripartum	
Others	Tachymopathies, myocardiopathies associated with conduction disorders

Table 2: Genes most frequently associated with familial DCM.

Gene symbol	Gene	Estimated frequency	Inheritance
TTN	Titin	25%	AutDom
LMNA *	Lamin A/C	6%	AutDom
MYH7	Myosin Heavy Chain 7	4%	AutDom
MYH6	Myosin Heavy Chain 6	4%	AutDom
MYPN	Myopalladin	3-4%	AutDom
FLNC *	Filamin C	2-4%	AutDom
TNNT2	Troponin T2, Cardiac Type	3%	AutDom
BAG3	BAG Cochaperone 3	3%	AutDom
SCN5A	Sodium Voltage-Gated Channel Alpha Subunit 5	2-3%	AutDom
MYBPC3	Myosin Binding Protein C 3	2%	AutDom
RBM20*	RNA Binding Motif Protein 20	2%	AutDom
TCAP	Titin-Cap	1%	AutDom
ACTN2	alpha-actinin-2	1%	AutDom
LAMA4	Laminin Subunit Alpha 4	1%	AutDom
LDB3	LIM Domain Binding 3	1%	AutDom
VCL	Vinculin	1%	AutDom
TMPO	Thymopoietin	1%	AutDom
PLN *	Phospholamban	<1%	AutDom
TMEM43 *	Transmembrane Protein 43		AutDom
DSP*	Desmoplakin		AutDom/Aut recessive

*= Considered high-risk genotypes (1)

AutDom = Autosomal dominant

CONCLUSIONS

DCM represents the final phenotypic expression of different types of myocardial injury. Given that different etiologies can cause the same disease, it is essential to achieve an appropriate study of the possible causes in each case. It is important to consider the possibility that a genetic alteration may be involved, since this is important in the indication of follow-up of family members and could have prognostic and therapeutic implications.

In addition to the initiation of timely and appropriate pharmacological therapy for each case, the ICD should be considered as a therapy for the prevention of sudden death. However, other elements, such as the identification of arrhythmogenic mutations in the genetic study or the extent of gadolinium uptake in the myocardium in magnetic resonance imaging, are beginning to be considered as risk predictors to help in the decision.

The identification of the final etiology of each DCM picture may have therapeutic implications. In certain specific etiologies, ongoing studies are being conducted with the objective of identifying new therapeutic approaches.

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