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## Dilated Cardiomyopathy: so many cardiomyopathies!

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# Dilated Cardiomyopathy: so many cardiomyopathies!

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*Dilated cardiomyopathy: a simple definition for a multifaceted disease*

The current definition of Dilated Cardiomyopathy (DCM) is relatively simple; namely, a heart muscle disease characterized by left ventricular (LV) or biventricular dilation and systolic dysfunction in the absence of either pressure or volume overload or coronary artery disease sufficient to explain the dysfunction [*1*]. In the last decades, the prognosis of patients with DCM has improved significantly with survival free from death and heart transplantation rising to more than 80% at 8-year follow-up [*2*]. This improvement in outcomes reflects the implementation of pharmacological and non-pharmacological therapeutic strategies, earlier diagnosis due to familial and sport related screening, and individualized long term follow-up with continuous re-stratification of risk.

Despite the relatively benign natural history overall, clinical management of patients and families with DCM is still challenging. DCM is currently the second most common heart failure phenotype and indication for heart transplantation, after ischaemic heart disease [*3*]. In fact, a non-negligible proportion of DCM patients still have an unfavorable prognosis, particularly in the short-term, with substantial heart-failure and arrhythmia-related risks. One reason for this is the complex and heterogeneous etiology of the disease [*4*]. DCM is an "umbrella" term that describes the final common pathway of different pathogenic processes and gene-environment interactions. There are many examples of Mendelian genetic disorders causing DCM, and it is probable that an individual genetic predisposition favors a dilated phenotype in the presence of trigger factors, such as inflammation, toxic insults from alcohol or drugs, and tachy-arrhythmias. DCM is also a feature of systemic disorders (i.e. autoimmune, endocrine, neuromuscular or infectious diseases, iron overload, sarcoidosis) that may be overlooked or diagnosed late in the course of disease. Distinguishing this complex etiological diversity is likely to result in better prognostic stratification and ultimately targeted therapy.



*Can a precise diagnosis influence therapeutic decisions?*

A thorough phenotyping and genotyping of DCM patients, through modern imaging techniques, such as speckle tracking echocardiography, cardiac magnetic resonance imaging, including a comprehensive tissue characterization analysis, and genetic testing on either selected gene panels or whole exome, represent the basis for the clinical management, but by themselves are often insufficient to define the aetiology. This requires better understanding of the complex interactions between environmental factors and genetic background, still an important gap of knowledge requiring focused research. A detailed etiological characterization of newly diagnosed DCM is crucial for clinical management aiming to improve outcomes of DCM patients, through the following different strategies:

- *Left ventricular reverse remodeling (LVRR) prediction:* DCM is a dynamic disease and LVRR is known as associated to better long- term outcomes [*4*], however the prediction of LVRR remains challenging. Etiological classification appears a pivotal tool, because DCM can undergo early and either significant or complete recovery after removal of the triggering insult, such as in the case of toxic/overload, infectious/inflammatory or chemotherapy/drug-associated forms[5-*8*]. Specific forms of inflammatory cardiomyopathies (such as giant cell, eosinophilic or sarcoidosis) have indication for early immunosuppression. In clinical practice, most of inflammatory cardiomyopathies derived from lymphocytic myocarditis. In those forms, recommendations to immunosuppression are based on expert opinions [*9*], rather than clinical trials. However, in inflammatory cardiomyopathies, the evidence of LVRR after an accurate diagnosis and treatment was associated to an excellent long-term prognosis [*6,10*]. Some reports describe particularly fast left ventricular reverse remodeling and a low rate of arrhythmic events in patients with DCM associated with hypertension [*11*]. Rhythm control in newly diagnosed DCM patients presenting with rapid and sustained supraventricular arrhythmias or frequent ventricular ectopy can lead to a reversal of cardiac dysfunction [5]. Similarly, correction of LV dyssynchrony induced by left bundle branch block with cardiac resynchronization therapy offers another route to recovery, particularly in the absence of likely pathogenic genetic variants or late gadolinium enhancement at

cardiac magnetic resonance [*12*]. Therefore, the identification of any possible removable trigger, should be systematically considered in the early management, and prognostication of DCM patients (**Figure**). In the absence of possible removable triggers, the detection of late gadolinium enhancement at cardiac magnetic resonance or specific mutations (such as cytoskeleton genes) are associated with lower probability of LVRR [*4*]. Finally, a red-flags approach, including a comprehensive multiparametric evaluation of the patient, should be systematically pursued in order to individualize the management [*4*].

- *arrhythmic risk stratification:* DCM patients are generally young (i.e. onset in 3$^{rd}$ to 5$^{th}$ decade of life) and barely symptomatic at diagnosis, thanks to early diagnosis due to systematic familial and sport activity screening programs. In these patients, the burden of life-threatening ventricular arrhythmias is particularly high in comparison to heart failure related events. Therefore, arrhythmic risk stratification remains challenging. The mono-parametric current risk stratification model, essentially based on severely depressed left ventricular ejection fraction, appears inadequate and an individualized multiparametric evaluation is warranted. Tissue characterization through a comprehensive cardiac magnetic study including late gadolinium enhancement presence and localization is emerging as a fundamental tool other than clinical parameters, ECG, Holter monitoring and echocardiographic findings [*3,4*]. Furthermore, the prognostic relevance of gene mutations in the setting of familial DCM is emerging. With the advent of next generation sequencing, the evidence that DCM is a genetic disease in a proportion of cases has strengthened [*13*] and large cohort studies are establishing important genotype-phenotype correlations. Beyond the widely known *LMNA* mutations, recently other genes (e.g. *FLNC, PLN, DSP* or *RBM20*) have been related to arrhythmic phenotypes, in so-called arrhythmogenic cardiomyopathy [*14-17*]. Mutations in the gene encoding titin appear to be most frequent and are associated with an arrhythmic phenotype and a particular susceptibility to environmental stressors [*18*].

- *Etiological treatments:* The definition of the precise genetic pathogenesis in many patients has shed light on the molecular mechanisms causing DCM and has stimulated research into new

treatments that directly target gene expression or the downstream pathways that mediate the disease [*19*]. Concurrently, advances have been made in the development of small molecules that can modulate the biophysical consequences of mutant proteins [*20*].

Despite gaps in knowledge, precision medicine in cardiology is no longer a theoretical vision, but a realistic opportunity for the future treatment of patients with DCM (**Figure**). The movement from symptomatic to treatments targeting specific disease mechanisms represents a conceptual shift from slowing disease progression to a paradigm of disease reversal or prevention as the main objective. A novel approach to DCM patients, including a comprehensive evaluation, from the identification of possible removal environmental triggers to the identification of likely pathogenic genetic variants, should be promoted in order to apply individualized therapeutic strategies.



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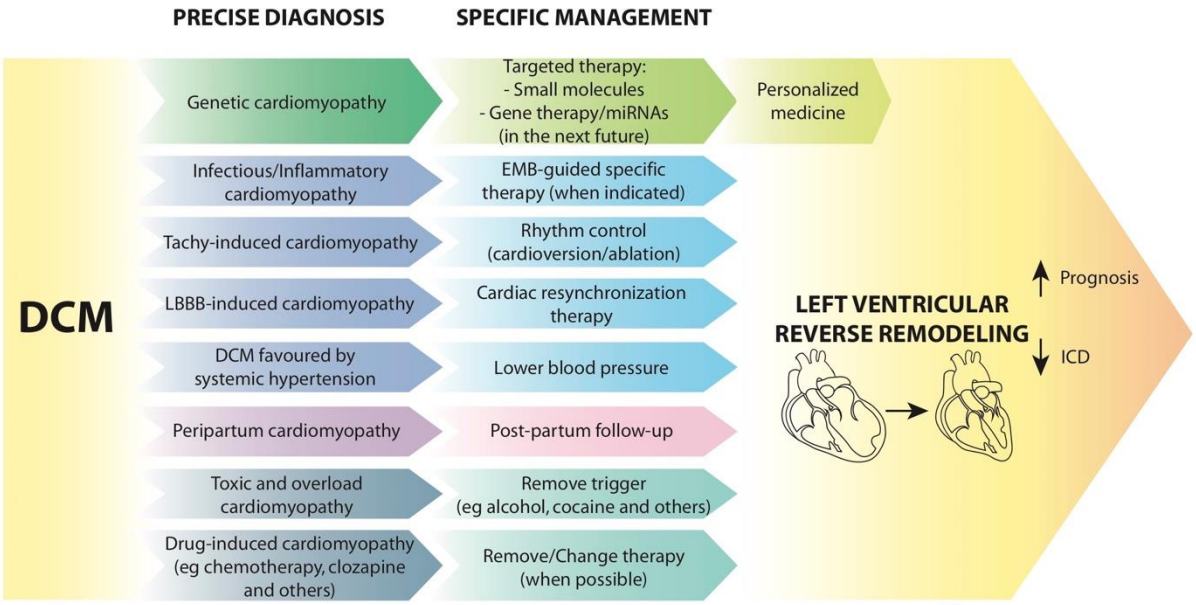
**Figure.** Specific treatments and possible prognostic benefit derived from precise diagnosis of DCM. Note the possible application of precision medicine in genetically determined DCMs , to be implemented in the next future.

*Legend. DCM: dilated cardiolmyopathy; ICD: implantable cardioverter defibrillator; LBBB: left bundle branch block.*



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