Dilated Cardiomyopathy

From Genetics to Clinical Management

Gianfranco Sinagra
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Antonio Cannatà, Davide Stolfo, Marco Merlo, Cosimo Carriere, and Gianfranco Sinagra

Abbreviations and Acronyms

ACEi	Angiotensin-converting enzyme inhibitors
ARBs	Angiotensin receptor blockers
CMR	Cardiac magnetic resonance
CPET	Cardiopulmonary exercise test
CRT	Cardiac resynchronization therapy
DCM	Dilated cardiomyopathy
EMB	Endomyocardial biopsy
FMR	Functional mitral regurgitation
ICD	Implantable cardioverter-defibrillator
LGE	Late gadolinium enhancement
LMNA	Lamin A/C
LVEF	Left ventricular ejection fraction
LVRR	Left ventricular reverse remodeling
RAAS	Renin-angiotensin-aldosterone system
SCD	Sudden cardiac death
TTN	Titin

Dilated cardiomyopathy (DCM) is a particular phenotype of heart failure, frequently with a genetic background, which affects mostly relatively young patients with low comorbidity. Patients affected by DCM are usually in their third/fifth decade of life

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and more frequently males (male/female ratio 3:1) [1]. It is a relatively rare disease (prevalence approximately 1:250); however, it requires difficult choices in terms of clinical management, device treatment, and indication to heart transplantation, thus emphasizing the role of an accurate prognostic stratification [2].

The Heart Muscle Disease Registry of Trieste enrolled so far more than 1500 patients with DCM, followed for more than 10 years, and represents the largest monocentric registry for this type of disease. The information obtained from the analysis of those data is crucial to understand the cornerstones of the management of patients with DCM. Yet from the early 1990s, significant improvements in prognosis of DCM patients have been achieved. Indeed, the yearly incidence of adverse events, death, or heart transplantation has been dramatically reduced to less than 2% per year, the incidence of sudden cardiac death (SCD) less than 0.5% per year, and a survival free from transplantation more than 87% at 8 years of follow-up [3, 4]. All these achievements are mainly due to several milestones reached in the management of DCM patients. Earlier diagnosis, etiological characterization, optimized medical therapy, and timely device implantation have been the main goals in this fight [2].

12.1 Prognosis of DCM: The Milestones of the Management

In the last decades, prognosis of DCM has dramatically been improved. The data from the Heart Muscle Disease Registry of Trieste perfectly highlight the results over time. Once believed as an irreversible disease, DCM has rapidly become a more treatable condition thanks to the advancements made. Analyzing three decades of enrollment of the Heart Muscle Disease Registry of Trieste is possible to underline the milestones reached in the management of DCM patients. In the late 1980s, treatment of patients with DCM was mainly symptomatic. Approximately one third of patients were treated with renin-angiotensin-aldosterone system (RAAS) blockade, and less than 15% of patients were treated with beta-blockers [5]. Neurohormonal blockade was yet at the beginning, and only a minority of patients received optimized medical treatment. With time, in the 1990s, treatment with angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs) and with beta-blockers became widespread. These improvements led to a significant shift upward of the survival curves, with a reduction of mortality of approximately 20% [5]. Finally, with the introduction of cardiac devices such as implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy (CRT), the incidence of SCD and the occurrence of life-threatening arrhythmias have been dramatically reduced with parallel prognostic improvements [5]. Therefore, proper management of DCM patients follows the guidelines on HF and requires multidisciplinary cardiologic approach among clinicians, invasive cardiologist, electrophysiologist, and noninvasive imaging specialists in order to optimize medical and device treatment for those patients.

12.2 Etiological Characterization as an Important Prognostic Factor

Etiological characterization of DCM is the hinge of clinical management, fundamental to improve the outcome of the disease. Ideally, patients with nonischemic DCM should undergo each and every diagnostic test to rule out potentially reversible causes of left ventricular dysfunction, which may benefit from specific therapeutic intervention. Several noxae may lead to a clinical phenotype of DCM. Among the most common causes, tachyarrhythmias (either frequent ventricular ectopy, ventricular tachycardia, or atrial tachyarrhythmias), elevated catecholamine level, or exogenous toxins, such as alcohol or cocaine, may be a reversible cause of DCM. Furthermore, systemic inflammatory syndromes, such as systemic autoimmune disorders (e.g., Churg-Strauss syndrome, sarcoidosis), and a significant history of arterial hypertension are common reversible causes of DCM [2, 4].

Severe left ventricular dysfunction can also be secondary to inflammatory cardiomyopathy. In this scenario, prompt diagnosis and timely management of post-myocarditis DCM or acute myocarditis with severe left ventricular dysfunction have significant prognostic implications. In those patients, a comprehensive integrated approach, including third-level diagnostic tools, such as cardiac magnetic resonance (CMR) and endomyocardial biopsy (EMB) in selected cases, should be systematically performed given their prognostic significance. Indeed, as recently reported, patients with post-myocarditis DCM have better outcomes compared to those with genetically determined DCMs [6–8].

Thus, differentiating between idiopathic DCM, genetically determined disease, and DCM of specific etiologies plays a fundamental role in the management and prognostic stratification. In the latter cases, nearly all patients experience favorable left ventricular reverse remodeling (LVRR) when the initial noxa has been dismissed or treated [2, 4]. Therefore, prognostic stratification should include proper etiological characterization and third-level analysis, such as CMR, and should systematically be performed in each and every patient with DCM from unknown cause.

12.3 DCM as a Dynamic Disease: The Importance of Follow-Up

DCM has been considered for a long time as an invariably irreversible condition. The cumulative experience derived from referral centers revealed that almost 40% of DCM patients under optimal medical and device treatments experience a significant left ventricular reverse remodeling [2–4, 9]. Optimal management of DCM is largely based on conventional therapy of systolic heart failure, according to current guidelines [10]. ACE inhibitors/angiotensin receptor blockers, beta-blockers, and mineralocorticoid receptor antagonists remain the cornerstone of DCM therapy. In persistently symptomatic patients fulfilling specific criteria, ivabradine may be advocated on top of medical therapy [10]. Despite the striking results of the

PARADIGM-HF trial and the data on the long-term outcomes in patients treated with LCZ-696 [11, 12], no data are available on the sacubitril/valsartan in the specific subgroup of patients with DCM.

Device treatment represents nowadays one of the pillars of the management of DCM patients. On the one hand, cardiac resynchronization therapy (CRT) is able to reduce mortality and improve outcomes of patients with DCM. On the other hand, the role of ICD in nonischemic cardiomyopathies is still controversial, and the correction of mitral regurgitation with MitraClip®, although can contribute to LV reverse remodeling (LVRR), has limited evidences from large series of DCM patients [2, 13–15].

From our experience, DCM natural history is characterized by improvement of ventricular involvement within 2 years from optimization of therapy, followed by a subsequent period of stability. As previously described, a complete LVRR within 24 months from the onset of the disease has been recently demonstrated as an independent prognostic tool [16]. CRT has been proven to positively influence LVRR, possibly inducing a persistent normalization of LV size and dimension specifically in DCM [17–20]. Noteworthy, identification of early markers of LVRR is still foggy highlighting the difficulties in prognostic stratification of those patients. However, patients without left bundle branch block (LBBB) at ECG [16] or late gadolinium enhancement (LGE) at CMR [21] are the most likely candidates to a favorable evolution of the disease.

12.4 Left Ventricular Reverse Remodeling Beyond the Left Ventricle

Besides LVRR, it is important to define specific and earlier features for prognostic stratification in DCM patients. Genetic background seems to have an impact on the prognosis of patients with DCM. The improved efficiency of genetic testing allowed better characterization of pathogenic mutations and their prognostic role. Mutations in lamin A/C (LMNA) have distinct genotype-phenotype correlations, requiring therefore specific treatments. Cytoskeleton and Z-disk mutations are associated with lower probability of LVRR, whereas mutations in gene encoding for desmosomal proteins and titin (TTN) mutations tend to have higher rate of LVRR. However, clear evidences on these scenarios should be further investigated [22].

Noninvasive assessments provide critical information of natural history of DCM. Hemodynamic indexes measured at echocardiography, i.e., improvement of functional mitral regurgitation (FMR) and right ventricular function, seem to foretell amelioration of ventricular function and thus LVRR. Those two indexes emerged already at a short time point of 6 months and represent early therapeutic targets and upmost useful tools for prognostic stratification in DCM [13, 14, 23]. The presence and the severity of FMR convey important therapeutic (i.e., percutaneous repair of mitral valve) and prognostic implications [13, 23], and right ventricular (RV) dysfunction along with the estimation of pulmonary arterial pressure is essential in the stratification of the disease [13, 23]. Furthermore, left ventricular diastolic function

and left atrial dimension should be systematically assessed for the estimation of left ventricular filling pressures and identification of restrictive filling pattern [24].

The definite identification of predictors of LVRR appears to be an important target for future researches, and the genetic background of LVRR appears to be the most interesting field to be explored. Therefore, echocardiographic evaluation of patients affected by DCM should be as much accurate as possible, beyond LV systolic function and dimensions, both at baseline and during follow-up. Newer noninvasive techniques assessing myocardial deformation (e.g., speckle-tracking echocardiography or CMR-derived strain) have greater sensitivity than Left Ventricular Ejection Fraction (LVEF) for identifying subclinical abnormalities of systolic function and may assume a role in the early detection of disease [2, 3, 25].

12.5 Prognostic Role of Cardiopulmonary Exercise Testing

DCM represents a specific model of HF characterized by relatively young patients with low comorbidity rate and a long asymptomatic history of disease, and these features may affect the traditional evaluation of symptomatic heart failure patients. In clinical management of DCM patients, this issue has always to be considered since it may influence the diagnostic and therapeutic workup. Cardiopulmonary exercise test (CPET), using peak of oxygen consumption, has driven the optimal timing for the selection of heart transplant candidates [26]. Due to the advances in knowledge of exercise impairment in HF, new indexes have been proposed, including the percentage of predicted peak VO_2, peak systolic blood pressure, and ventilatory efficiency, expressed as VE/VCO_2 slope [2, 3, 27–29]. Notably, patients affected by DCM perform better at CPET compared to other etiologies of HF due to their intrinsic characteristics; therefore the abovementioned markers need further future validation in DCM. Recently predicted VO_2% and VE/VCO_2 slope emerged as the strongest CPET predictors in a large cohort of DCM, with cutoffs of 60% and 29%, respectively [30]. Validation in prospective series is advocated, but it is clear that the etiology of HF is fundamental in interpreting the parameters of CPET for candidates to heart transplant [30].

12.6 Arrhythmic Risk Stratification

In the last years, ICDs dramatically reduced the risk of SCD and mortality in patients with reduced ejection fraction HF on optimal medical treatment [10]. However, in patients with nonischemic cardiomyopathies, the real benefits of ICD implantation appear disputable [15, 31, 32]. Although ICD implantation dropped the mortality rate in young and mildly symptomatic patients with DCM [5], ICD indication for primary prevention of SCD is largely based on the severity of systolic dysfunction [10, 33]. However, approximately 50% of SCD occur in patients without severely reduced LVEF [34]. Therefore, it appears crucial a more accurate characterization of the arrhythmic risk in DCM patients (Fig. 12.1) [35].

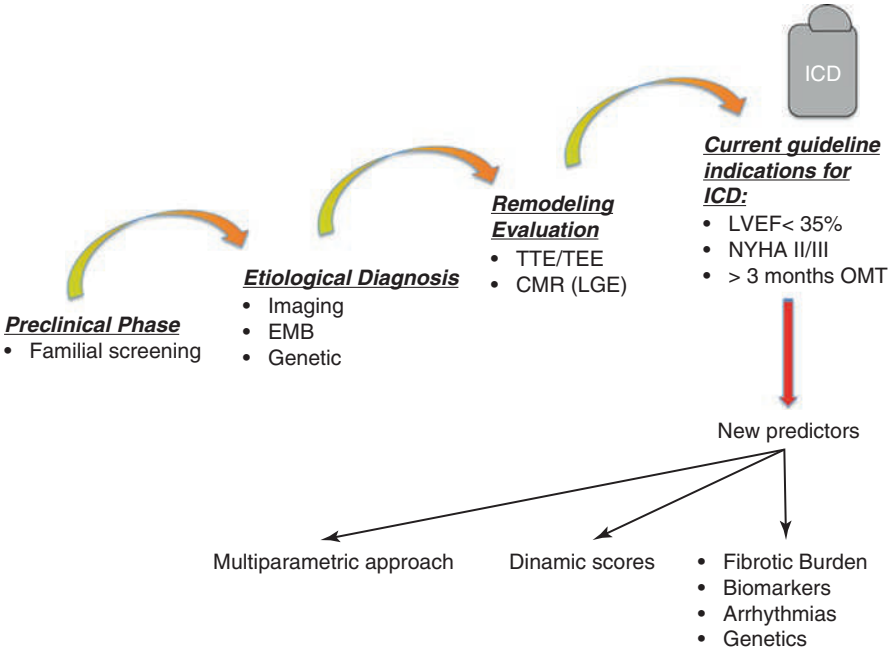

Fig. 12.1 Arrhythmic risk evaluation and the need for novel predictors in DCM. *CMR* cardiac magnetic resonance, *EMB* endomyocardial biopsy, *LGE* late gadolinium enhancement, *LVEF* left ventricular ejection fraction, *NYHA* New York Heart Association, *TEE* transesophageal echocardiogram, *TTE* transthoracic echocardiogram

Furthermore, early arrhythmic stratification in DCM patients may encase important prognostic features. Indeed, solely one third of cases on optimal medical therapy, admitted with the criteria for ICD implantation, maintain those criteria over a 6-month follow-up [19]. The occurrence of LVRR has important prognostic implications in particular in those candidates for ICD implantation in primary prevention. Accordingly, a wait-and-see period of about 3–9 months on optimal medical therapy is recommended before the ICD implantation [2, 10, 33]. However as showed by Losurdo et al., approximately 2% of patients with DCM die suddenly in the first 6 months after the diagnosis [36]. Unfortunately, there are not yet definitive predictors of early arrhythmic events. A severe LV dilatation at baseline with prolonged QRS duration and a long duration of symptoms seem to be useful tools in identifying high-risk patients [36]. Moreover the familial history of SCD, the history of probable cardiac syncope, or the presence of highly arrhythmic expression at Holter ECG monitoring could identify arrhythmogenic DCM at elevated risk of SCD [37]. Further data are required to confirm these findings. In the next future, techniques as CMR and specific genetic tests could help for better identification of patients at higher risk [2, 21, 38].

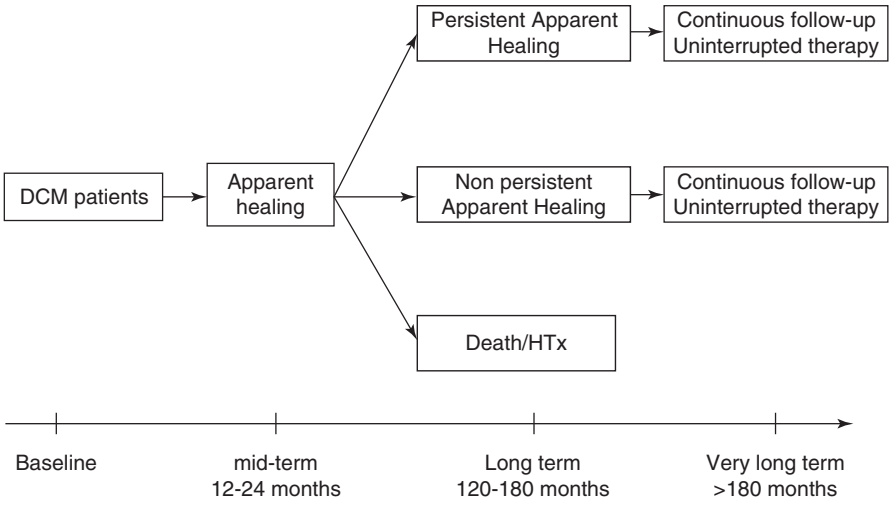

Fig. 12.2 Proposed follow-up time points to assess apparent healing. *DCM* dilated cardiomyopathy, *HTx* heart transplantation

12.7 The "Apparent Healing" Phenomenon

Approximately 15% of patients with DCM on optimal medical treatment normalize their LV size and function persistently over 10 years of follow-up. However, over a very long-term follow-up (15 years), a non-negligible percentage (5%) of patients with persistent "apparent healing" as a consequence of progressive deterioration of left ventricular function underwent CRT-ICD implantation, died for refractory heart failure, or needed cardiac transplantation [2, 3, 5, 39]. Therefore, at the current state of knowledge, the treatment should be continued lifelong and also in apparently stable/healed DCM patients (Fig. 12.2).

12.8 Uninterrupted Follow-Up and Continuous Reclassification of the Disease

Optimal treatment of patients with DCM has significantly increased the survival rates and has resulted in long periods of clinical stability. Data from the registries highlighted that from the sixth to eighth year of follow-up, a new progression of the disease may occur [2, 4, 39], indicating the pivotal role not only of an accurate and complete initial diagnosis but also of a continuous, individualized, and long-term follow-up evaluation in DCM patients (Table 12.1). In everyday clinical practice, DCM patients of more than 50–60 years of age and with duration of the disease of more than 10 years are more often seen. In those patients systematic reassessment of risk factors and continuous reclassification of the disease is mandatory (Fig. 12.3).

Table 12.1 Important time points in the natural history of DCM

Time	Evaluation
Baseline	• Complete evaluation (noninvasive and invasive, if necessary) in order to assess an etiological characterization, to decide timing of individualized follow-up and timing and type of therapeutic strategies • Administration of optimal medical treatment
3–9 months	• "Hemodynamic" reverse remodeling (improvement of mitral regurgitation; normalization of right ventricular systolic function; improvement of diastolic dysfunction) • Consider ICD/CRT-D implantation • Attention to the onset of negative prognostic factors[a]
24 months	• Left ventricular reverse remodeling completed • Attention to the onset of negative prognostic factors[a]
72–84 months	• Possible progression of the disease after stability induced by medical therapy • Reclassification of the disease in the presence of progression of the disease (attention to possible onset of possible causes of left ventricular dysfunction: hypertension; diabetes; ischemic heart disease; structural valve disease) • Attention to the onset of negative prognostic factors[a]
After 120 months	• Need of continuing follow-up and therapy lifelong in order to early detect signs of progression of the disease in the long term • Attention to the onset of negative prognostic factors[a]

CRT-D cardiac resynchronization therapy defibrillator, *ICD* implanted cardioverter-defibrillator
[a]*Negative prognostic factors*: atrial fibrillation; right ventricular dysfunction; left ventricular bundle branch block; functional mitral regurgitation

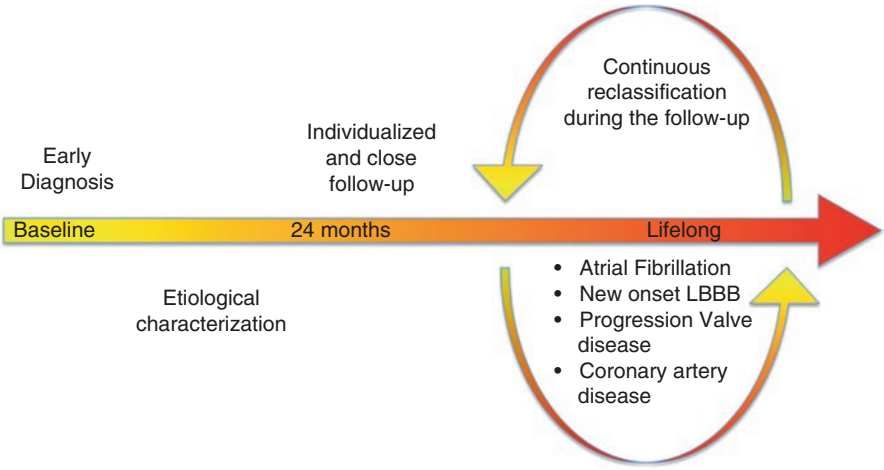

Fig. 12.3 Key point in DCM management. *LBBB* left bundle branch block

Abrupt deterioration of LV ejection fraction or progressive LV dilation as well as new onset of significant arrhythmic burden could be related to the progression of the disease but also to the development of coronary artery disease; hypertensive heart disease, structured valve disease, or acute myocarditis should be ruled out given their prognostic relevance in the natural history of the disease (Fig. 12.4) [2, 3].

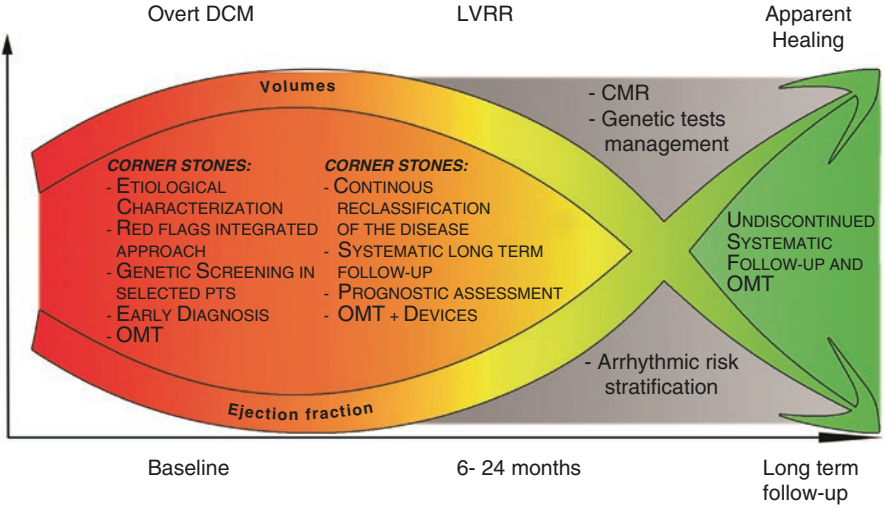

Fig. 12.4 The importance of follow-up in DCM patients [2]

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