Contemporary etiology and prognosis of dilated non-ischemic cardiomyopathy

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ABSTRACT

Non-ischemic dilated cardiomyopathy (NI-DCM) represents a specific etiology of systolic heart failure that usually affect young individuals with a genetic background in up to 40% of cases. Behind the term NI-DCM there is a spectrum of different diseases, and an accurate etiological classification appears pivotal for the clinical management and prognostic stratification of these patients. In the last years the prognosis of NI-DCM patients dramatically improved thanks to the progresses in medical treatment/ device therapy and earlier diagnosis especially in familial context. In this review we summarize the actual state of art in the management of these patients. In the era of precision medicine, a lot of progresses have been made to expand our knowledge on the management of NI-DCM patients. A complex interaction between genotype and external triggers is the main determinant of the clinical phenotype in NI-DCM, and a lot of efforts must be done by clinicians to systematically rule out all the possible causes involved in the pathogenesis. Progresses in cardiac imaging and familial screening led us to detect subtle abnormalities in the initial phase of the disease and also helped us to furtherly stratify the prognosis and arrhythmic risk of these patients. It is plausible that a more precise etiological classification will be needed in the near future. NI-DCM contains a spectrum of different diseases. Proper etiological classification, early diagnosis and strict follow-up are essential to tailor care of these patients.

KEY WORDS: Cardiomyopathies; Heart failure; Review.

To date, non-ischemic dilated cardiomyopathy (NI-DCM) is defined on a phenotypic point of view as a left or biventricular systolic dysfunction, often associated with dilation, in the absence of abnormal loading conditions or significant coronary artery disease.[1, 2] Once believed as the final pathway of several heart diseases, nowadays, NI-DCM represents a distinct clinical phenotype serving as a starting point for clinicians to better define the etiology, the underlying molecular and genetic mechanisms and, possibly, the personalized therapy. The concepts related to NI-DCM as a primary heart disease are progressively evolving and the notions coupled with the novelties available nowadays to clinicians were not even present in the textbooks just a few years ago. Over the last decades basic and clinical science tried to investigate the mechanisms and the causes of this extremely complex and heterogeneous disease.[1]

Furthermore, NI-DCM was previously considered as a rare disease. However, the actual

prevalence ranges from 1/2500 to 1/250 people, with a male to female ration of 3:1. In up to 40% of the cases an identifiable genetic background can be found.[3] The real prevalence of NI-DCM remains partially underestimated. Recent data suggested that NI-DCM might be responsible for 7.9% of unselected HF hospital admissions,[4] with a prevalence close to 50% in patients with non-ischemic HF.[5]

Although progresses in medical treatment and device therapy significantly improved the prognosis of NI-DCM patients in the last decades,[6, 7] pump failure remains the main cause of death in NI-DCM, and the disease is one of the leading causes of heart transplantation (HTx) in the western world.[8]

Patients affected by NI-DCM are younger and carry less comorbidities in comparison to those with other HF etiologies,[5] with a higher rate of left ventricular reverse remodeling (LVRR) on optimal medical treatment and device therapy.[9] This makes the arrhythmic stratification particularly challenging in clinical practice. Finally, it has to be taken into account that, despite LVRR, a further functional deterioration due to the progression of the illness, or the advent of new incipient factors, might compromise the prognosis of these patients in the long-term natural history.[10, 11]

During the last years, many efforts towards a precise etiological definition and personalized prognostic stratification of NI-DCM patients have been made, and progresses in cardiovascular imaging and genetic screening paved the way to an era of precision medicine in NI-DCM.[12-16]

This review aimed to highlight the above crucial novel and evolving aspects of the clinical management of NI-DCM patients, with a particular focus on the need of a deep etiological classification, which might help clinicians to tailor care. Some issues such as the arrhythmic risk and prognostic stratification, the role of cardiovascular imaging, the genotype-phenotype correlation and the need of a strict individualized follow-up are also discussed.

One name, a miscellaneous of diseases!

The term NI-DCM is often used in clinical practice to identify HF patients without documented ischemic etiology and obvious reversible factors such as hypertension, valve disease and congenital heart disease.[7] Only few studies stressed the importance of identifying underappreciated triggers that might be responsible for left ventricular systolic dysfunction (LVSD) in NI-DCM (Table I).[7, 10, 17-31]

Environmental factors play indeed a crucial role in the development of NI-DCM and they should be systematically investigated while approaching these patients:

- following acute myocarditis, up to 25-30% of patients develop overt LVSD culminating in NI-DCM,[17] requiring endomyocardial biopsy to confirm the diagnosis;[18]
- furthermore, chemotherapy agents (mostly Anthracyclines) are known for their functional and structural damage on the myocardium, which is largely irreversible,[19] while other toxic substances (*e.g.* alcohol, cocaine) might be responsible for potentially reversible form of NI-DCM;[20, 21]
- fast supraventricular arrhythmias or a high burden of ventricular ectopy promote progressive LVSD inducing NI-DCM. Fast arrhythmias are another potentially reversible condition in which NI-DCM is induced or mediated by atrial or ventricular arrhythmias.[22] In these cases, the diagnosis might be complicated as frequently arrhythmias and NI-DCM are diagnosed simultaneously;
- heart involvement is also present in some autoimmune diseases (*e.g.* Churg–Strauss syndrome and sarcoidosis) with peculiar clinical presentations and therapeutic implications;[23]
- peripartum cardiomyopathy is a specific form of NI-DCM with deterioration of cardiac function typically between the last trimester of pregnancy and up to 6 months postpartum, associated with a higher prevalence of LVRR in the subsequent course.[7]

Once all possible known triggers have been ruled out, a genetic etiology is more likely, especially in the context of a positive family history for NI-DCM or SCD.[32] In the last series, a genetic background has been found in up to 40% of NI-DCM patients, with more than 50 causative genes involved.[33] Most patients affected by NI-DCM have an autosomal dominance inheritance, but X-linked, autosomal recessive and

maternal transmission are also described. *TTN* gene (encoding for titin) is the most frequently described gene, accounting approximately for 20% of all genetically determined NI-DCM, but so far many other genes encoding for sarcomeric proteins, cytoskeleton, nuclear envelope, sarcolemma, ion channels and intercellular junctions have been implicated in NI-DCM.[33]

Importantly, specific red flags could emerge at the clinical evaluation and might suggest a genetic etiology, also in sporadic cases.[8] Puzzling information derived from a comprehensive evaluation, from family history to LGE patterns at cardiac magnetic resonance, through ECG, Holter ECG monitoring, echocardiogram and biomarkers, are crucial to identify a possible genetic background of any specific NI-DCM. For example, *LMNA* gene mutations (encoding lamin A/C) are usually associated with cardiac conduction disturbances, and in some cases with concomitant elevation of serum creatine-kinase levels and possible skeletal muscle involvement (limb–girdle or Emery–Dreifuss muscular dystrophy).[34] DMD gene mutations (encoding for dystrophin) are frequently characterized by an ECG pattern with a posterolateral or inferolateral 'pseudonecrosis'[35]. Furthermore, other genetic variants (e.g. *LMNA, RBM20, FLNC, DSP, PLN*) have been lately demonstrated to be characterized by a propensity to ventricular arrhythmias and by antero-lateral negative T waves and low QRS voltages at ECG.[36-38]

A complex interplay between genotype and environment

The fascinating interplay between genotype and environment is progressively gaining prominence in the evaluation of NI-DCM patients, and the clinical implication of a precise diagnosis is becoming always more relevant. Indeed, late evidence suggests that genetic backgrounds and external stressors work together in determining the clinical phenotype of NI-DCM patients.[14]

TTN gene represents the paradigm of this aforementioned interplay. *TTN* mutations have been indeed related to subclinical phenotype of NI-DCM, where only the presence of an external cardiac stressor finally leads to HF manifestations.[39] Moreover, truncating *TTN* variants are also seen in the general population, leaving doubts on the real pathogenicity of *TTN* in absence of external factors.[39]

At the same time, a genetic background could be evidenced in patients affected by secondary forms NI-DCM. The presence of *TTN* mutations in patients with alcohol related NI-DCM has been linked to a more severe disease presentation,[24] and, appealingly, a genetic pathogenic mutation was demonstrated in approximately 30% of patients with a biopsy-proven active myocarditis.[40]

Furthermore, the presence of a particular genetic background, mainly represented by specific *TTN* mutations, seems to confer a higher risk of chemotherapy induced NI-DCM.[41]

Ultimately, a similar prevalence of truncating variants in 8 genes was seen in a series of peripartum cardiomyopathy patients compared to a control cohort of genetically determined NI-DCM, suggesting a shared genetic predisposition in the two conditions. Even in this observation, TTNtv were the most prevalent mutations.[25]

These observations bring some important implications because of a complex interplay of mutually non-exclusive etiologies. In these patients, a complete workup must be always performed to put together all the elements involved in determining the clinical phenotype. Indeed, a proper etiological characterization aids not only tailored therapy or the removal of extrinsic factors, but also carries an important prognostic burden, representing one of the main evolving field in the management of NI-DCM patients.[31]

Clinical presentation and specific phenotypes in NI-DCM

In the oldest series, NI-DCM patients typically presented with signs and symptoms of HF.[42] More rarely, thromboembolic events or sudden cardiac death (SCD) were described as the first manifestation (Figure 1).

Interestingly, compared to other non-selected HF etiologies, NI-DCM patients tended to have a lower left ventricular ejection fraction (LVEF) and a more significantly impaired functional status (prevalence of New York Heart Association (NYHA) Class III-IV) at the first clinical presentation.[4]

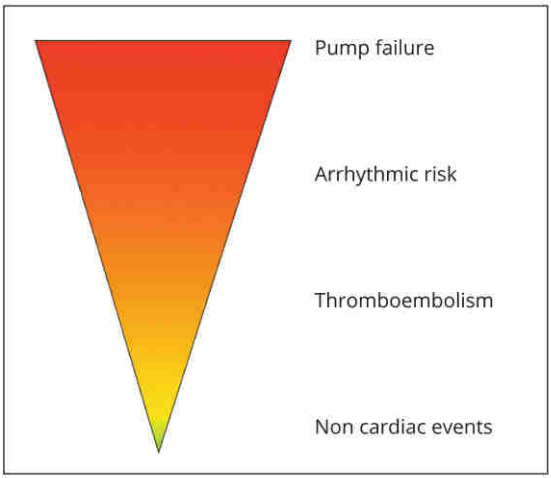

Figure 1.—Risk-grading of clinical events in NI-DCM.

During the last decades, early diagnosis and progresses in the genetic screening mainly in the context of familial forms, led us to observe often early or pre-clinical phases of the disease. Those patients, despite an importantly remodeled LV, are mostly asymptomatic or scarcely symptomatic[2] and are significantly exposed to arrhythmic events, particularly in the context of specific genetic etiologies.[33]

Besides the typical echocardiographic phenotype of dilated and hypokinetic heart, a specific hypokinetic non-dilated phenotype has been lately included in proposed new definition of NI-DCM.[2] Finally, up to 20% of NI-DCM patients present a mid-range LVEF (*i.e.* 40-to-50%), especially in the modern era. This could represent the result of an earlier diagnosis with timely introduction of medical treatment. These patients are usually associated with an overall better prognosis compared to those who present with severe systolic impairment, but must be strictly followed in the clinical course as a percentage of them can evolve in forms with severe LVSD despite optimal medical treatment (OMT).[43] However, in the context of specific features such as severe diastolic dysfunction or non-sustained/sustained ventricular arrhythmias, NI-DCM presenting with mid-range LVEF can indicate some aggressive forms of disease with a rapid evolution to end-stage disease in which aggressive therapeutic strategies should be employed.[44]

Changing mortality in NI-DCM: the dynamic nature of the disease

The overall prognosis of NI-DCM patients has significantly improved in the last decades.[6] The two cornerstones responsible for this improvement are the progresses in the HF medical treatment and device therapy,[45] together with the constant efforts toward an always earlier and more precise diagnosis.[7] Paradigmatically, a disease who had a 10 years survival free from adverse events of approximately 40% in the late 1970s, now sees almost 80% of patients free from major cardiovascular outcomes in the same timeframe.[6]

Death due to end-stage HF is still the leading cause of mortality in NI-DCM patients, while the rate of SCD has importantly declined in the contemporary era, with an actual yearly risk of 0.15%.[6]

However, as stated above, the term NI-DCM includes a series of different diseases and many efforts need to be made for a tailored prognostic stratification in the single patient.[7] Indeed, different etiologies of the disease carry specific prognosis, which appears to be benign in secondary extrinsic forms, such as tachycardia-induced NI-DCM, or more adverse such as in chemotherapy-induced NI-DCM.[6] Interestingly, together with the improvement in overall prognosis, a step rise in non-cardiac related events, as competing risk of death, has been observed.[6] This notion is of pivotal relevance as tailored medical and device therapy significantly reduced cardiac events, exposing patients to longer lifetime and higher incidence of non-cardiac-related conditions ultimately leading to death.[6]

Several factors have been demonstrated to be independently associated with better prognosis in NI-DCM and resemble the dynamic nature of this disease when adequately treated.

• LVRR, defined mostly by an absolute increase in LVEF ≥10% (or absolute LVEF at follow-up ≥50%), associated with a relative reduction in indexed left ventricular end-diastolic diameter ≥10% (or absolute value at follow-up ≤33 mm/m^2), represents the most important goal in the treatment of NI-DCM patients, and is achieved in almost 40% of cases during

24 months of OMT.[9] Indeed, patients achieving a full LVRR have a striking benefit in term of prognosis compared to the others.[9, 11] At the same time, the natural progression of the disease or new incipient factors can lead to a subsequent deterioration of LVEF, also in the specific subgroup of "apparently healed" patients (*i.e.* patients with recovered LVEF >50% under therapy), with a consequent poorer outcome.[11] Unfortunately, at the moment, no reliable scores are available to predict LVRR and single parameters have been reported such as the absence of LGE or LBBB.[9, 46] Even less data are available on the predictors of a subsequent functional deterioration in previously recovered patients.[11]

• The presence of right ventricular dysfunction (RVD) negatively impacts on the prognosis and the response to medical treatment of NI-DCM patients.[47] However, in most of cases RVD is only expression of hemodynamic impairment at the first clinical presentation and it recovers already during the first 6 months of OMT, preceding the LVRR.[47] In some cases, a long-term involvement of right ventricle (RV) might be seen in the natural progression of the disease, conferring a poor prognosis.[48]

• Moderate to severe mitral regurgitation (MR), especially if persistent after the implementation of the drug and device therapy, is usually the expression of forms of more advanced disease with an important hemodynamic compromise and is associated with poorer cardiovascular outcomes.[49]

• Left bundle branch block (LBBB) is present in up to 1/3 of NI-DCM patients, with a higher prevalence in non-genetic forms, and it confers a lower likelihood of LVRR in response to OMT.[9] The development of LBBB during the late course also emerged as an independent predictor of all-cause mortality.[50] However, in some cases LBBB might be responsible for NI-DCM in the so called "dyssynchronopathy" which has specific characteristics, such as usually lack of late gadolinium enhancement on cardiac magnetic resonance (CMR) or pathogenic genetic variants, and has a brilliant response to cardiac resynchronization therapy (CRT) with a full cardiac recovery[26] (Table I).

• The onset of atrial fibrillation (AF) during follow-up is expression of a structural disease and negatively impacts the prognosis of NI-DCM.[51] Interestingly, recent observations suggest that permanent vs. persistent/paroxysmal AF confer a markedly worse outcome, encouraging clinicians to rhythm control strategy in NI-DCM to possibly avoid the evolution in permanent AF forms.[52]

• Late gadolinium enhancement documented by CMR is clearly associated with worse prognosis and higher risk of SCD.[12] Even though the extent and localization of LGE and its association with adverse outcomes is still debated, in the era of precision medicine CMR should be performed in all NI-DCM patients to provide pivotal information in patients' characterization and management. The possible role of repeating CMR during the clinical course to monitor the disease progression remains to be established.

• Female sex constantly emerged as an independent protective prognostic factor in NI-DCM.[53-55] The reasons of a better prognosis in females are still partially unknown and might dwell in some intrinsic factors specifically related to the female sex.[56, 57] Late experiences demonstrate that the response to OMT is similar in males and females, with comparable rate of LVRR after 24 months. However, the occurrence of LVRR seems to confer a stronger prognostic benefit in females in comparison to their male counterpart, while the differences between sexes might be diluted in patients without LVRR and in the presence of specific genetic backgrounds.[53, 54]

Clinical applications of standard and advanced imaging in NI-DCM: beyond the left ventricular ejection fraction

The role of cardiac imaging progressively gathered more relevance in any cardiovascular condition throughout the last decades and in the specific setting of HF and cardiomyopathies.[58] Indeed, in the setting of HF overall, cardiac imaging allows clinicians to categorize patients in the appropriate HF phenotype (*i.e.* HFrEF, HFpEF or HFmrEF).[59] In the specific setting of NI-DCM cardiac imaging should be particularly accurate. Indeed, if we merely consider the systo-diastolic performance and the severity of valvular dis-

TABLE I.—*Etiological classification of NI-DCM.*[7, 10, 17-30]

External triggers of NI-DCM		
Etiology	Mechanisms and involved etiological factors	Clinical implications
Post-myocarditis	Inflammatory myocardial damage caused by viruses (prevalent), bacteria, protozoa, helminths, fungi, toxic agents[17]	Endomyocardial biopsy required to confirm the diagnosis[18] Immunosuppressive therapy in selected cases[27, 28]
Chemotherapy-induced	Anthracyclines (prevalent), alkylating agents, proteasome inhibitors, Her2-targeted therapies, vascular endothelial growth factors inhibitors[19]	Dose dependent toxicity, cause-effect relationship Accurate anamnesis crucial for the identification
Alcohol-induced	No clear data on the amount of alcohol intake needed to produce the cardiac toxic effect[21] Important genetic predisposition[24]	Need for a prompt diagnosis. Higher rate of left ventricular reverse remodeling after alcohol abstinence[21]
Cocaine-induced	Myocyte apoptosis, impaired intracellular calcium handling, eosinophilic myocarditis[20]	Usually in the late stage of cocaine abuse Myocardial infarction and arrhythmias in the anamnesis.
Tachy-induced	Supraventricular arrhythmias; high burden of premature ventricular complexes/ventricular non-sustained arrhythmias[22]	Medical treatment directed to the suppression/control of the arrhythmic burden Consider ablation in refractory cases[30]
Left bundle branch block-induced dyssynchronopathy	Ventricular dyssynchrony, diastolic dysfunction, consequent mitral regurgitation[26]	Usually lack of LGE in cardiac magnetic resonance Great response to cardiac resynchronization therapy[26]
Cardiac involvement in autoimmune disease	Sarcoidosis, Churg-Strauss, sclerodermia, dermatomyositis[7, 23]	Muscle/skeletal disorders, other organs involvement[7] Bradyarrhythmias and typical septal involvement in cardiac sarcoidosis[23]
Metabolic and endocrine dysfunction	Thyroid abnormalities, Cushing disease, phaeochromocytoma[10]	Mainstay of the treatment is the correction of the metabolic and endocrine abnormalities
Peripartum cardiomyopathy	Vascular insult caused by anti-vascular or hormonal effects of late pregnancy and the early postpartum period[25]	Late pregnancy or the early postpartum period. Usually a documented genetic predisposition[25] High rate of left ventricular reverse remodeling Promising results with the use of bromocriptine[29]

TABLE II.—*Clinical and prognostic meaning of baseline and follow-up evaluation of imaging data.*[9, 52, 61-68]

Echocardiographic parameter	Clinical utility	Evolution and clinical and prognostic significance
LVEF[9]	Diagnosis, prognostic stratification, therapeutical implications	Dynamic change, prognostic re-stratification
LVEDV[9, 61]	Diagnosis, prognostic stratification, etiological diagnosis, disease duration, selection of patients for mitra-clip	Dynamic change, prognostic advantage in LV reverse remodeling
Left atrial volume[52, 64, 65]	Disease duration, prognostic marker, AF risk	Unknown long-term evolution, possible prognostic stratification
LVGLS[62, 63]	Diagnosis in familial DCM without overt disease, prognostic marker	Unknown long-term evolution, possible prognostic stratification
Mitral regurgitation[66]	Prognostic information, selection of patients for mitra-clip	Highly dynamic parameter, decompensation marker
RV systolic function[67, 68]	Diagnosis, prognostic stratification, etiological diagnosis	Possible improvement in medical therapy with prognostic implications

LVEF: left ventricular ejection fraction; LVEDV: left ventricular end-diastolic volume; RV: right ventricle; LVGLS: left ventricular global longitudinal strain; LV: left ventricle; AF: atrial fibrillation; DCM: dilated cardiomyopathy.

ease we would miss relevant information that could be helpful in the precise definition and in the clinical management of NI-DCM patients[60] (Table II).[9, 52, 61-68] Echocardiography should be considered alongside ECG features that could provide insights regarding the etiology and the prognosis of NI-DCM. Particularly, electrocardiographic predictors of adverse outcome in NI-DCM are considered left ventricular (LV) hypertrophy criteria, anterolateral T wave inversion, T wave alternans and QRS fragmentation.[69, 70] The paramount importance of echocardiography emerges at various stages of the clinical work. Indeed, from the familial screening, echocardiography allows to detect even initial stages of LV dilation and/or cardiac dysfunction.[71] Moreover, recent evidence showed that speckle-tracking echocardiography allows to detect earlier abnormalities in apparently healthy relatives, in the setting of genetically determined NI-DCM. This can be useful to predict the development of clinically overt NI-DCM even in the absence of structural heart adverse remodeling.[72, 73] In this perspective, it might be useful to always consider LV deformation parameters when assessing relatives of genetic NI-DCM patients. An early administration of neurohormonal therapy could provide important prognostic benefits.[71] Echocardiography at first assessment of clinically overt NI-DCM also provides other inalienable information. The presence of acute LV systolic dysfunction with normal or slightly increased LV volumes are highly suggestive of an acute inflammatory myocardial disease.[72] The presence of thinned interventricular septum, LV motion abnormalities not fitting with any coronary artery disease pattern and non-ischemic posterolateral LV aneurysms are suggestive of cardiac sarcoidosis[61] and dystrophine-related NI-DCM respectively (Figure 2).

Moreover, it was well established that echocardiographic parameters are very helpful to predict the long-term outcome of NI-DCM patients. Alongside conventional echocardiographic assessment, advanced echocardiography imaging tests showed to be helpful in predicting the outcome in patients with NI-DCM. LV longitudinal strain analysis was proven to have an incremental diagnostic accuracy on top of LVEF.[62] Advanced echocardiography is also useful to predict the response to CRT; indeed, specific strain patterns were associated to increased im-

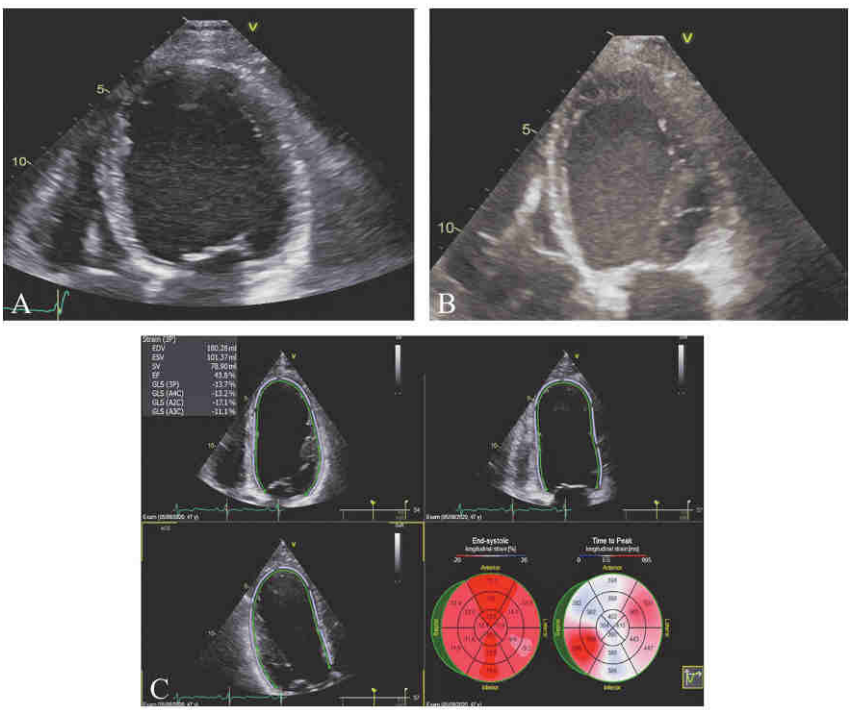

Figure 2.—Clinical application of echocardiography in NI-DCM: A) severely dilated left ventricle in a patient with a history of anthracycline intake; B) mildly dilated left ventricle in a patient with a mutation in the *LMNA* gene; C) global reduction in left ventricular global longitudinal strain in a patient with a moderate systolic dysfunction.

provement in LVEF.[63] Beyond the left ventricle, an accurate cardiac ultrasound was shown to be able to provide helpful prognostic information with possible therapeutic implications. Left atrial size and function, as previously shown in HF overall, are markers able to identify patients at higher risk of adverse outcome and incidence of AF during the follow-up.[64, 74] The role of LA on cardiac outcome in these patients is likely to be linked to two different processes: LA adverse remodeling due to HF syndrome, mostly in terms of fluid overload, increased LV filling pressure and MR, and a primary cardiomyopathic process regarding LA cardiomyocytes.[65] Another fundamental prognostic information that could be obtained by conventional echocardiography is the multiparametric assessment of MR. Indeed, LV dilation and systolic dysfunction are two factors that exponentially increase the risk to determine a significant MR in absence of a significant LV valve organic disease.[66] Differently from general HFrEF, NI-DCM patients are affected by a primary cardiomyopathic process that could involve any cardiac chamber, including RV. The presence of RVD in absence of advanced left heart disease is explained by the fact that NI-DCM recognize in many cases a genetic etiology and various genetic mutations were shown to be responsible of RVD even at the beginning of the disease.[67] Advanced echocardiography focused on the evaluation of RV strain in NI-DCM was shown in small retrospective analyses to be incremental on RV function conventionally assessed.[68] Finally, considering that NI-DCM is a dynamic disease, the RV systolic impairment should be considered not only at baseline but also during the follow-up, in order to identify which patients are going through an adverse clinical course and those who got benefit from medical therapy.

Despite echocardiography represented for many decennials the gold standard for the imaging in NI-DCM, nowadays, the role of CMR is rapidly growing up. The most important advantage carried by CMR over standard echocardiography is the possibility to obtain a structural characterization of the tissue *in vivo* (Figure 3).[75, 76] This feature allows to better define the precise etiology of NI-DCM and to improve the prognostic stratification. In acute myocarditis, the presence of increased signal intensity on

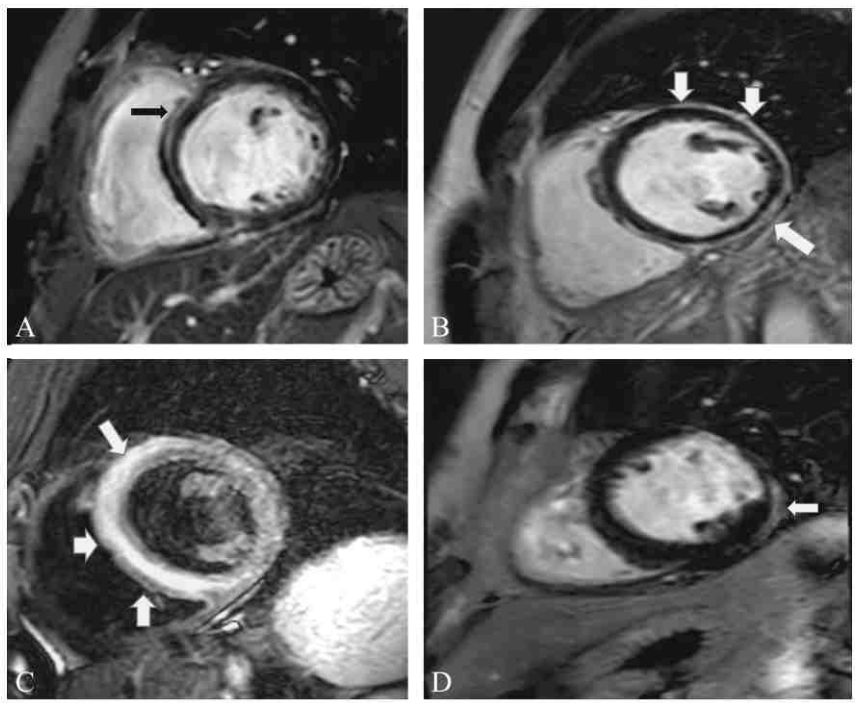

Figure 3.—Utility of cardiac magnetic resonance in NI-DCM: A) intramural late gadolinium enhancement (LGE) in the septal wall (black arrow) in a patient with a previous acute myocarditis; this location of LGE has been documented to confer a high risk of life-threatening cardiac events;[75] B) diffuse inferoposterolateral subepicardial late gadolinium enhancement (white arrows) in a patient affetcted by NI-DCM due to *FLNC* mutation; C) diffuse myocardial edema in a STIR sequence (white arrows) in the acute setting of myocarditis; D) atypical transmural LGE with a thinning of the anterolateral wall (white arrow) in a patient with a diagnosis of NI-DCM in the absence of coronary artery disease.

T2-weighted images is a specific sign of presence of oedema and, therefore, an active inflammatory process.[77] After gadolinium injection, if a chronic fibrotic process was established in the muscle, an hyperintense signal would appear in the segment of interest.[77] Approximately 30-45% of NI-DCM patients are found to have LGE and its presence, together with other advanced CMR parameters, is associated with reduced rates of LVRR and increased risk of adverse outcome.[16, 78] In this perspective, the role of CMR appears paramount, since previously it has been challenging to detect LVRR predictors. Moreover, the high space resolution of CMR allows classifying as subendocardial, mesocardiac or subepicardial the fibrotic scar, providing a further diagnostic and prognostic help. The vast majority of patients shows a mesocardiac or subepicardial LGE pattern, while a minority (15-20%) show subendocardial scar.[79] Another advantage carried by the high special resolution is the possibility to identify the number and the localization of the myocardial fibrotic segments; the presence of septal LGE was associated with increased risk of death in retrospective analyses, while the presence of concomitant septal and lateral LGE identified patients at risk of major ventricular arrhythmias.[80] On the other hand, the quantification of LGE did not show to be able to provide the same clinical relevance.[80] The role of CMR is also useful in the prediction of response to CRT. Indeed, patients with radiological findings of posterolateral LV scar have a reduced chance to adequately respond to CRT implantation.[81] Finally, CMR was show to have a paramount clinical utility in distinguish athletes heart from initial stages of cardiomyopathy.[75]

Genetics in NI-DCM: when to perform a genetic test? Prognostic value and clinical implications

The frontier of genetics in NI-DCM is rapidly growing in the last years, and the role of genetic testing is acquiring more and more importance for its clinical and prognostic implications.[82] According to guidelines,[83] genetic testing should not routinely drive the diagnosis, but could be helpful in the diagnosis of selected borderline or doubtful cases, or when its result can lead to a decision, particularly in presence of red flags in personal or family history. In the clinical practice, genetic test should be performed in DCM cases without a clear etiology, after having accurately excluded common causes of dilated phenotype (ischemic heart disease, hypertension, myocarditis, toxic, tachycardia).[7] Due to the suboptimal sensitivity of a known familial history in the identification of familial (or genetic) DCM, sporadic forms should be also considered for genetic testing especially in presence of particular phenotypic manifestations. As stated in the guidelines genetic testing is recommended also for first-degree relatives, starting from age of 10-12 years, when a specific mutation is identified in the proband,[83] although earlier testing could be considered in laminopathies. A specific flow-chart for genetic testing is described in Figure 4.[72]

While in the recent past the role of genetic screening was mostly confined to an earlier diagnosis in the context of family members, growing evidence is progressively available that document specific clinical implications of particu-

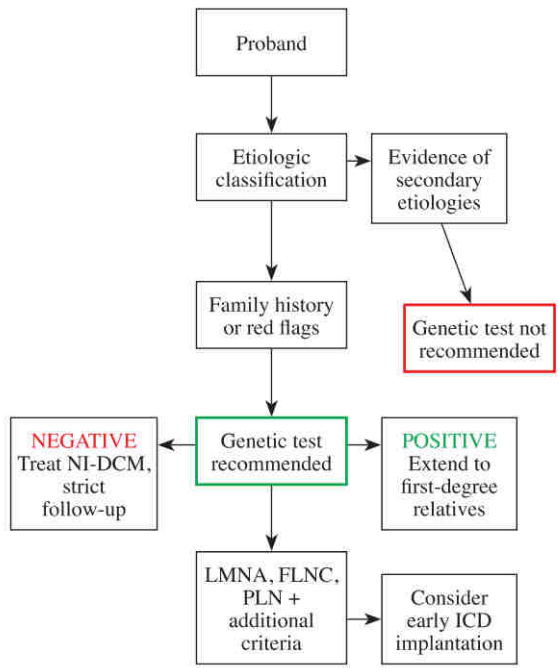

Figure 4.—Flow chart of genetic screening in DCM probands and relatives (modified from Paldino *et al.*).[72]

lar genetic backgrounds also in NI-DCM probands.[14, 16] While the most commonly associated variants in NI-DCM are the pathogenic *TTNtv*, the genetic landscape of NI-DCM is quite broad. In this setting, specific pathogenic variants might contribute to the development of distinct phenotypes.

In the last years, several genes have been identified with a particular propensity to arrhythmic phenotypes in NI-DCM:[22]

- *LMNA* gene mutations were the first ones to be deeply characterized, and clear preponderance of arrhythmic presentations and a higher documented risk of SCD in comparison to other forms of NI-DCM led to propose a lower threshold for cardiac defibrillator implantation in these patients, especially in the presence of specific high-risk features.[34, 84] These findings opened a new era in the management of NI-DCM patients, with a prospective of tailored therapeutic approach in different genetic background;
- filamin C (encoded by *FLNC* gene) is an actin cross-linking protein that provides structure for the sarcomere and is one of the largest Z-disc proteins. Its mutations were initially related to skeletal myopathies and hypertrophic/restrictive phenotype, but recently it has been demonstrated that some *FLNC* splicing variants can be connected with aggressive and arrhythmic forms of NI-DCM;[38]
- mutations in *PLN* gene (encoding for phospholamban) lead to biventricular forms of NI-DCM with associated high risk of malignant ventricular arrhythmias, especially in populations from the Netherlands;[85]
- desmosomal gene mutations, originally thought to be almost only related to forms of arrhythmogenic right ventricular cardiomyopathies (ARVC), in fact involves the LV in a predominant number of cases, with an even isolated LV involvement in a significant number of patients with desmoplakin (*DSP*) cardiomyopathy.[86] These forms are also associated with a preponderance of major ventricular arrhythmias, comparable to *LMNA* forms;[36, 87]
- recent series of patients with a documented mutation in the cardiomyocyte-specific RNA splicing factor RBM20 have been described to be affected by highly penetrant and arrhythmogenic forms of NI-DCM;[37]
- lastly, variants of *TTN* have been described as associated with forms of NI-DCM more prone to achieve LVRR on optimal medical treatment with respect to other genetically determined DCM,[67] with a subsequent possibly lower arrhythmic risk.

All these findings led to the institution of the term "arrhythmogenic cardiomyopathy", which includes some genetic forms of cardiomyopathies characterized by marked arrhythmic preponderance[87] and represents an important overlap between ARVC and NI-DCM (Figure 5). In the last consensus on the management of this entity, a lower threshold for cardiac defibrillator implantation was proposed also for *FLNC* and *PLN* mutations, amplifying the tailored approach for genetic NI-DCM besides *LMNA*.[87]

In the next years is plausible that a more comprehensive characterization of all the NI-DCM causative genes will be available, with always more therapeutic implications in the individual management of these patients.

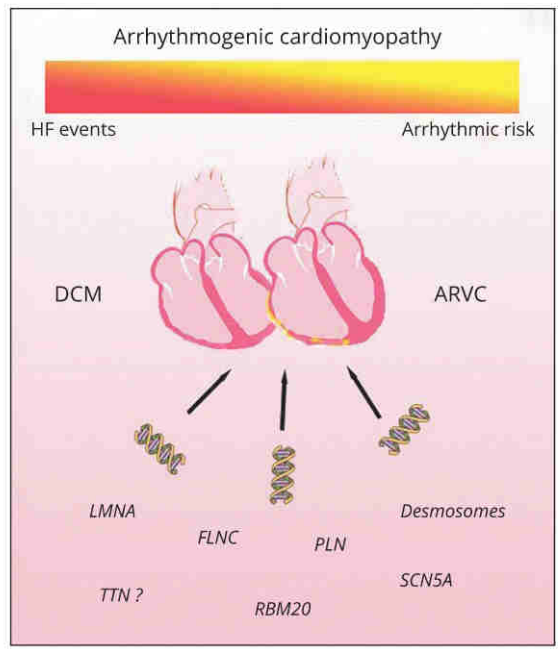

Figure 5.—NI-DCM and ARVC frequently share the risk of arrhythmic events at follow-up. The genetic background in common between these two apparently differently disease define the common etiology and clinical evolution.

Therapeutic options: time for a tailored approach?

The general mainstay of treatment in NI-DCM is represented by guideline-directed therapies of chronic HFrEF.[45] Indeed, drugs and device therapy actually employed in the HF treatment, including the recently introduced angiotensin-neprilysin inhibitors (ARNI), sodium/glucose cotransporter 2-inhibitors (SGLT2i), have been demonstrated to confer an important prognostic benefit regardless the etiology of HF[5, 45, 88]

However, some considerations regarding device therapy and some etiology-specific treatments should be mentioned. In terms of device therapy, an unsolved debate on whether implantable cardiac defibrillators (ICDs) might improve the prognosis of NI-DCM patients has raised after the apparent neutral results of DANISH Trial.[27] This trial reflects on one-side the absolute risk reduction in SCD of NI-DCM patients in the last years,[6] but, at the same time, might lead to some non-specific conclusions that might be misleading for clinicians. As already aforementioned, the tailored approach should be the current and future road in a so heterogeneous disease, and the appropriate selection of ICD candidates should go through an individual patient assessment based on competitive risks and specific etiological/genetic background.

In this perspective, some relevant results have been reported for some etiology-specific treatments in NI-DCM, reinforcing the importance of an accurate diagnosis.

Immunosuppression with prednisone and azathioprine was associated with improved cardiac function at 6 months and improved long-term transplant-free survival in patients affected by inflammatory virus negative cardiomyopathies.[28, 89] In this view, the most recent consensus papers recommend to perform an endomyocardial biopsy in case of suspected acute myocarditis presenting with cardiogenic shock, major ventricular arrhythmias, refractory heart failure or high-degree atrioventricular block associated to LV systolic dysfunction.[29, 30] Other clinical scenarios do not usually require a hystological sample, since the procedural risk is not balanced by the possible therapeutic advantage. The clinical implication of histological findings is that, in the acute phase, the immunosuppressive therapy is advised whenever histological inflammation seems to be the main cause of the cardiac manifestation. However, there is not agreement about indication to viral search. Indeed, evidences regarding immunosuppression and viral presence in the acute phase still lack. After the acute phase, viral search is recommended due to its potential to detect enterovirus, cytomegalovirus, and adenovirus presence. These patients should be considered for immunosuppression therapy withdrawal. On the other hand, in patients with Parvovirus B-19 and Herpes virus-6 the decision on the maintenance of immunosuppression might be taken according to the initial response to immunosuppression (troponin and LVEF trends) or to the viral load.[29] Finally, some evidence suggests that patients whose myocardial tissue is positive for Herpes Virus-6 or Enterovirus may benefit from specific therapy (*i.e.* aciclovir and interefer-on beta, respectively), while immunoglobuln therapy was proven to be neutral in myocarditis with Parvovitus B-19 persistence.[90] Anakinra, an IL (interleukin)-1β blocker, has also raised interest for showing potential beneficial effects on hemodynamic, inflammation, and clinical performance in patients with inflammatory cardiomyopathy, even though more robust evidence is needed before the implementation of this drug in the contemporary treatment of NI-DCM.[91] Moreover, some evidence suggest a possible beneficial effect of immunoadsorption in NI-DCM, even though, despite the long duration of this research, the improvement was shown only on minor endpoints (e.g. functional improvement); therefore, more research is needed before the introduction of this therapeutic approach in clinical practice[92] Similarly, a small clinical trial showed the potential benefit carried by mesenchymal cell administration in NI-DCM but nowadays current evidences do not support adequately the treatment to allow to introduce it in clinical practice.[93] Another specific therapy focused on the prevention of NI-DCM is the prophylactic therapy with Dexrazosane in patients scheduled for chemotherapy. Retrospective meta analysis showed a potential benefit of this approach, but prospective trials are warranted to better define this issue.[94]

In peripartum cardiomyopathy, the use of bromocriptine on the side of standard HF therapy showed improvement in LVEF and prognosis in a randomized multicenter clinical trial.[95] However, these results were less evident in some other series, and a placebo-controlled trial of bromocriptine for peripartum cardiomyopathy is needed.

Finally, in some forms of NI-DCM with associated supraventricular arrhythmias, AF ablation emerged as a possible disease modifier, with a significant reduction in the rate of heart failure hospitalizations and a significant LVEF improvement after successful ablation.[96] This result has been recently confirmed in a cardiac MR study, showing that NI-DCM patients in whom LV dysfunction was not related to other causes than AF, catheter ablation was effective in improving LVEF in the short term, especially in patients without LV fibrosis.[97]

Unfortunately, at the moment, no available therapeutic options directly targeting the molecular processes driven by specific gene mutations in NI-DCM are available, however this represents the real goal for the future. In this scenario, interesting results are available in preclinical settings in the *LMNA* gene. Indeed, *LMNA*-mutated mice show typical molecular changes with consequent increased cardiac activity of the ERK1/2, JNK, and p38 MAP kinases. Interestingly, when mice were treated with the p38 inhibitor ARRY-371797, it prevented LV dilation and deterioration of LVEF.[98] A current international phase 3 clinical trial is ongoing (NCT03439514) and will investigate the benefit of ARRY-371797 on change in 6-minute walk distance at 12 weeks in 160 patients with symptomatic NI-DCM caused by a *LMNA* gene mutation. This trial will be the first one directly involving genotype-specific therapy, and will hopefully open new frontiers in the treatment of NI-DCM patients.

The challenging arrhythmic risk stratification: the emerged issues

Defining the risk of life threatening arrhythmias in NI-DCM patients is a challenging issue in the prognostic stratification.[99] Indeed, differently from ischemic HFrEF, the arrhythmic risk in these patients results to be difficult to be assessed in consideration of the considerable number of variables involved in the arrhythmias pathogenesis[100] (Table III).[7, 69, 70, 91, 95-100] The first and most intuitive feature currently assessed is the LV systolic performance. Indeed, patients with an important reduction in LVEF (*i.e.* <35%) combined with the presence of HF symptoms (*i.e.* NYHA >1) are considered at high risk of adverse arrhythmic outcome.[99] This conception directly derived from the SCDHeFT trial.[101] However, as previously shown in retrospective analyses, it seems to not be accurate enough to estimate the risk of arrhythmic events assessing only the LVEF and the functional status.[102] Specifically, it has been demonstrated that LVEF is an independent predictor of adverse arrhythmic outcome even in asymptomatic patients.[102] On the other hand, the DANISH trial demonstrated that ICD implantation in non-ischemic HFrEF did not result in a clinical benefit in terms of overall survival.[27] However, study population was heterogeneous and the predicted arrhythmic risk was low. In particular, the subgroup analysis showed a significant prognostic advantage in younger patients implanted with an ICD; this result points out the needing for a precise classification of NI-DCM, since it is likely that older population, characterized by a higher comorbidity burden have a lower risk of sudden death compared to younger patients carrying specific high-arrhythmic genotypes. This consideration claims for future trial addressed towards precision medicine,

TABLE III.—*Factors associated with major ventricular arrhythmias in NI-DCM.*[7, 69, 70, 91, 95-100]

Clinical predictors	Etiology[91]
	Functional status[95]
	Family history[7]
	Previous syncope[7, 91]
	Genetics[96]
	Gender[91, 96]
Imaging	LVEF[91, 95]
	LGE (pattern and localization)[99, 100]
Electrocardiography	Frequent ventricular extrasystole[97]
	Non-sustained VT[97]
	Wide QRS[100]
	Fragmented QRS[69]
	Negative T waves[70]
	Heart rate turbulence[98]

LVEF: left ventricular ejection fraction; LGE: late gadolinium enhancement; VT: ventricular tachycardia.

taking in account the specific etiology together with all the risk factors for incident major ventricular arrhythmias in NI-DCM.

Regarding the specific features of NI-DCM, the etiology of non-ischemic LV systolic dilation and dysfunction could be a useful predictor of arrhythmic events occurrence during the follow-up. While tachycardia-induced HFrEF are considered as low risk cardiomyopathies in terms of sudden cardiac death risk, patients with genetically-determined NI-DCM are considered a high-risk population.[102] The electrical activity of LV, explored by surface ECG and Holter ECG is a useful tool to better stratify the arrhythmic risk. Indeed, a prolonged, fragmented or low voltage QRS and presence of negative anterolateral T waves identify patients at higher risk of sudden death.[41] Concerning Holter ECG, non-sustained ventricular tachycardia and a burden of ventricular extrasystole >1000/day and an increased heart rate turbulence are linked with the risk of ventricular arrhythmias and sudden death.[103, 104]

LGE was shown to be a powerful predictor of sudden cardiac death or ICD intervention in NI-DCM patients, both in patients with LVEF <35% and in patients with LVEF >35%.[105] Moreover, the combination of the width of QRS complex and the presence of LGE in CMR is an independent event predictor.[106] Unfortunately, despite all this information, nowadays a specific treatment, a part from ICD implantation, was not investigated yet, claiming for more basic and clinical research. Moreover, it should not be forgotten that NI-DCM is a dynamic disease. Indeed, the contemporary survival of these patients is long enough to allow the disease to evolve and develop new features that could help in reclassify the arrhythmic risk.[6] Even the genetic background could assume a different meaning throughout the follow-up. Indeed, some genetic variations may be re-classified thanks to ongoing research and, consequently, new information about the arrhythmic risk of the single patients could be gathered. Moreover, the functional status may change many times during a decennial follow-up with consequent different indications for ICD. Patients may experience AF incidence, LVEF may drop, LBBB might develop, the ventricular arrhythmic burden may increase and renal function may worsen.[11, 50, 51] In this perspective it is fundamental to reassess the arrhythmic risk at each follow-up visit and whenever a negative feature appears.

Long-term evolution of the comorbidity burden

Nowadays, the life expectancy of new-onset NI-DCM may be of many decades.[6] Considering that mean age of new-onset NI-DCM patients is definitely lower compared to HFrEF overall, usually patients' clinical assessment is not burden by a severe comorbidity profile.[107] However, during the long-term follow-up, a consistent number of patients may develop other comorbidities, such as chronic obstructive pulmonary disease, liver disease or kidney failure.[6] Indeed, the incidence of kidney failure or chronic obstructive pulmonary disease may reduce the chance of the patients to tolerate disease modifying drugs (renin angiotensin system inhibitors and beta blockers, respectively).[108, 109] In this perspective, the clinical cardiologist caring cardiomyopathic patients should be aware of this possibility and should therefore be ready to early detect new-onset comorbidities during the follow-up. Finally, patients with NI-DCM are exposed to the risk of developing other cardiac disease that could worsen the clinical course of the primary disease. Therefore, incident coronary artery disease, inflammatory cardiomyopathy or primary valvular disease should always be excluded when a clinical worsening emerges, without an underlying cause. The other side of the coin is represented by patients who normalize the cardiac function, reaching a LVEF >50%. In these patients it was shown that withdrawal neurohormonal therapy increases the risk of a new worsening of the disease.[110] However, emerging evidence suggests that diuretic therapy might be safely withdrawal in selected stable HFrEF patients.[111]

Is it time for a new classification, beyond the phenotype?

Any complex medical conditions require an appropriate classification, in order to better define any single patients and identify the best treatment. However, the complex scenario of NI-

DCM faced in the past with different types of classifications, but nowadays no one satisfied the clinical needing.[7] Two distinct classifications have been independently proposed in the first 2000's from the American Heart Association and the ESC. For the AHA, cardiomyopathies are classified as primary myocardial disorders or secondary heart disease and are segregated according to their genetic or non-genetic etiologies.[112] The ESC, instead, defines cardiomyopathies as "myocardial disorders in which the heart muscle is structurally and functionally abnormal, in the absence" of secondary causes.[1] Recently, the WHO has proposed a novel revised classification based on the genotype-phenotype nomenclature of Cardiomyopathies, and its attempt is to clarify many of the critical issues of this complex subset of diseases (7): the MOGES classification.[113] This classification provides a comprehensive assessment of the patients and its aim is to depict all the characteristics of any cardiomyopathy. The assessment and the categorization of the patient takes place in five steps:

- M (morpho-functional phenotype): stands for the morphologic phenotype of the cardiomyopathy (dilated in the specific setting of NI-DCM);
- O (organ/system involvement): stands for the presence of damage in organs other than the heart (for example muscle involvement in Duchenne disease);
- G (genetic inheritance pattern): assesses the presence of the same disease in the family and the transmission pattern;
- E (etiology): in this section, first it is made a distinction between genetics and non-genetics, secondly, it is performed a subsequent distinction on the specific cause in non-genetics cases (i.e. myocarditis, drugs, etc.);
- S (status): in this section it is provided the functional status of the patients (*i.e.* NYHA class, AHA state).

As foreseeable, due to its complexity, the disadvantage of this kind of classification is the low feasibility to apply it in clinical practice, even though in specialized centers caring cardiomyopathies all these aspects are considered.[113]

Despite the numerous attempts, a unifying classification able to comprehend all aspects of NI-DCM is still lacking. Therefore, a new cardiomyopathies classification is claimed, even though it is clear that combining simplicity and efficacy in a so much complex disease will be challenging. It would be desirable that the new classification will take in consideration the emerged knowledge, in terms of genotype-phenotype interaction, new technologies, big data information and artificial intelligence systems that may progressively address any patient toward a specific and targeted management.

Conclusions

All the efforts made towards earlier diagnosis and tailored treatment of patients with NI-DCM along with the advances in genetic screening boosted our knowledge of the basic mechanisms leading to overt NI-DCM and the conditions undermining apparently normal hearts. Therefore, always more effort should be committed in the direction of a complete characterization of the different phenotypes of NI-DCM toward preventive interventions and targeted therapeutic approaches. In the era of precision medicine, tailored approach to each single patient from diagnosis to specific treatment is required to improve their outcomes and ameliorate their quality of life.

Key messages

- Non-ischemic-dilated cardiomyopathy (NI-DCM) represents a specific model of systolic heart failure with a genetic background in up to 40% of cases. Behind the term NI-DCM, there is a spectrum of different diseases, and every effort should be performed by clinicians toward a precise etiological classification and a proper individualized management.
- Progresses in the knowledge of different genetic backgrounds and the progressively larger availability of advanced cardiac imaging paved the way to an era in which tailored treatments are possible for NI-DCM patients.
- An unifying classification able to comprehend all aspects of NI-DCM is still lacking and is claimed in the near future to help clinicians in the approach of the disease.

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