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ESC REPORT

Proposal for a revised definition of dilated cardiomyopathy, hypokinetic non-dilated cardiomyopathy, and its implications for clinical practice: a position statement of the ESC working group on myocardial and pericardial diseases

Yigal M. Pinto[1]*, Perry M. Elliott[2], Eloisa Arbustini[3], Yehuda Adler[4], Aris Anastasakis[5], Michael Böhm[6], Denis Duboc[7], Juan Gimeno[8], Pascal de Groote[9,10], Massimo Imazio[11], Stephane Heymans[12,13], Karin Klingel[14], Michel Komajda[15], Giuseppe Limongelli[16], Ales Linhart[17], Jens Mogensen[18], James Moon[19], Petronella G. Pieper[20], Petar M. Seferovic[21], Stephan Schueler[22], Jose L. Zamorano[23], Alida L.P. Caforio[24], and Philippe Charron[25,26]

[1]Departments of Cardiology and Experimental Cardiology, Academic Medical Hospital (AMC) at the University of Amsterdam, Amsterdam, The Netherlands; [2]Inherited Cardiac Diseases Unit, The Heart Hospital, University College London, London, UK; [3]Center for Inherited Cardiovascular Diseases, IRCCS Foundation Policlinico San Matteo, Pavia, Italy; [4]Management, The Chaim Sheba Medical Center, Tel Hashomer, The Sackler School of Medicine Tel Aviv University, Tel Aviv, Israel; [5]First Cardiology Department, University of Athens, Medical School, Athens, Greece; [6]Klinik für Innere Medizin III, Universitätsklinikum des Saarlandes, Homburg, Germany; [7]Assistance Publique Hôpitaux de Paris (AP HP), Hôpital Cochin, Université Paris Descartes, Paris, France; [8]Department of Cardiology, University Hospital Virgen de Arrixaca, Murcia, Spain; [9]Service de cardiologie, Pôle cardio-vasculaire et Pulmonaire, CHRU de Lille, Lille, France; [10]Inserm U1167, Institut Pasteur de Lille, Université de Lille 2, Lille, France; [11]Cardiology Department, Maria Vittoria Hospital and University of Torino, Torino, Italia; [12]Cardiovascular Research Institute Maastricht, Department of Cardiology, Maastricht University Medical Center, Maastricht, Netherlands; [13]ICIN, Netherlands Heart Institute, Utrecht, Netherlands; [14]Department of Molecular Pathology, Institute for Pathology, University Hospital Tübingen, Tübingen, Germany; [15]INSERM UMRS-956, UPMC Univ Paris 6, AP-HP, Hôpital Pitié-Salpêtrière, Paris, France; [16]Division of Cardiology, Monaldi Hospital, Second University of Naples, Naples, Italy; [17]Second Department of Medicine, Department of Cardiovascular Medicine, General University Hospital and the First Faculty of Medicine, Charles University, Prague, Czech Republic; [18]Department of Cardiology, Odense University Hospital, Odense, Denmark; [19]Division of Cardiovascular Imaging and Biostatistics, The Heart Hospital, London, UK; [20]Department of Cardiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; [21]Department of Cardiology, University Medical Center, Belgrade, Serbia; [22]Department of Cardiology, Freeman Hospital, Newcastle upon Tyne, UK; [23]Cardiac Imaging Unit, Ramón y Cajal University Hospital, Madrid, Spain; [24]Division of Cardiology, Department of Cardiological Thoracic and Vascular Sciences, University of Padova, Padova, Italy; [25]Université de Versailles-Saint Quentin, Hôpital Ambroise Paré, AP-HP, Boulogne-Billancourt, France; and [26]AP-HP, Hôpital Pitié-Salpêtrière, Paris, France

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In this paper the Working Group on Myocardial and Pericardial Disease proposes a revised definition of dilated cardiomyopathy (DCM) in an attempt to bridge the gap between our recent understanding of the disease spectrum and its clinical presentation in relatives, which is key for early diagnosis and the institution of potential preventative measures. We also provide practical hints to identify subsets of the DCM syndrome where aetiology directed management has great clinical relevance.

Keywords Dilated cardiomyopathy • Position statement • Heart failure

Introduction

Research over recent decades has shed new light on the aetiology and natural history of dilated cardiomyopathy (DCM).[1–8] In particular, it is recognized that many patients have a long preclinical phase characterized by few if any symptoms and minor cardiac abnormalities that fall outside current disease definitions.[1,2,5,9–12] It is also clear that distinct subtypes in fact share a common DCM phenotype.[13–19] The aim of this position paper was to update the definition of DCM to take into account its diverse aetiology and clinical

* Corresponding author. Tel: +31205664927, Fax: +31206976177, Email: y.pinto@amc.uva.nl

manifestations in patients and relatives. We do not describe the general management of left ventricular systolic dysfunction as this is covered in existing European Society of Cardiology (ESC) heart failure guidelines[20] but do consider the implications of an aetiology oriented approach to therapy.

Causes of dilated cardiomyopathy

Dilated cardiomyopathy is currently defined by the presence of left ventricular (LV) or biventricular dilatation and systolic dysfunction in the absence of abnormal loading conditions (hypertension, valve disease) or coronary artery disease sufficient to cause global systolic impairment.[5] The causes of DCM can be classified as genetic or non-genetic[5] (*Table 1*), but there are circumstances in which genetic predisposition interacts with extrinsic or environmental factors.

Genetic causes

Large population studies report an increased risk of disease in the offspring of patients with non-ischaemic heart failure similar to that seen in other complex genetic traits.[21] Dilated cardiomyopathy can also appear to be inherited as a monogenic trait with autosomal-dominant, X-linked, autosomal-recessive, and matrilinear modes of transmission.[1,2,5,22–24] In the pre-molecular era, systematic cardiac screening of the relatives of patients with DCM identified probable familial disease in about 20–35% of cases.[11,24,25] Subsequently, more than 50 disease-related genes have been reported (main genes in *Table 1*),[7] although relatively few are supported by robust segregation analyses or experimental data. Sequencing studies using small and medium size panels of genes identify potentially causative mutations in about 20–25% of affected cases, with lamin A/C and cardiac sarcomere genes the most frequently reported.[26,27] With the advent of high-throughput low-cost sequencing technologies, analysis of many more genes, including large genes such as titin, has become feasible[28] and suggests that mutations in TTN are most frequent in DCM,[29] although it remains to be confirmed that truncating mutations in TTN are always pathogenic.

Increasingly, studies using high-throughput platforms report the presence of more than one potentially causative mutation in patients with DCM.[30] While many are probably silent variants, a new model of oligogenic inheritance (i.e. a disease caused by a small number of mutations in more than one gene) is emerging that poses considerable challenges for genetic counselling and predictive testing. This may provide one explanation for the sometimes dramatic variation in disease penetrance seen in some individual families. From a clinical perspective, careful phenotypic evaluation of patients and their families is crucial for the correct interpretation of genetic results.[30]

Non-genetic causes

Drugs and toxins

A number of chemical compounds can induce DCM, the most common of which are excess alcohol consumption and chemotherapeutic agents (see *Table 1* and Supplementary material online, *Table S1*).

Alcoholic cardiomyopathy is often overlooked and suggested in some studies to account for 21–32% of DCM (reviewed in ref. 31). Alcohol causes LV systolic dysfunction in a dose-related manner and some studies suggest reversibility upon abstention. Other toxins can cause immediate LV dysfunction or many years after exposure. It often resolves following withdrawal of the drug or toxin, but can persist for many years in a subclinical form. In the case of alcohol and some drugs such as anthracylines, there appears to be individual susceptibility that relates to genetic and non-genetic mechanisms.

Myocarditis

Myocarditis is a recognized cause of DCM and the current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis has been summarized in a recently published position statement.[30] The diagnosis of myocarditis is based on a suspicious clinical presentation combined with endomyocardial biopsy (EMB) confirmation (by histology, immunohistology, and molecular evidence for infection). Biopsy-proven myocarditis may be reversible if the acute inflammatory process heals and the cause (for example, viral infection) resolves, but in up to 30% of cases it can progress to DCM.[3] In a proportion of familial and non-familial pedigrees, infection-negative myocarditis, with or without a DCM phenotype, is an organ-specific autoimmune disease occurring in genetically predisposed individuals.[9] In such cases, symptom-free relatives may exhibit serum organ-specific anti-heart antibodies (AHA),[9–11] that are associated with more frequent mild left ventricular abnormalities and predict progression to DCM.[9–11]

Peripartum cardiomyopathy

Peripartum cardiomyopathy (PPCM) is a rare but potentially life-threatening disorder defined by the development of unexplained systolic heart failure towards the end of pregnancy or in the months following delivery.[32] A number of associations are reported including Afro-Caribbean ethnicity, older age, multiparity, multiple pregnancy, and hypertension with or without pre-eclampsia. The aetiology is complex and includes autoimmunity, foetal microchimerism, virus infection, stress activated cytokines and toxicity caused by an abnormal cleavage product of prolactin (recently reviewed in ref. 33). As in other apparently acquired causes of DCM, genetic predisposition seems important in some cases, with a recent report of familial DCM co-existing with PPCM or identification of DCM causative mutations in some PPCM women.[19]

Combined effects

The above aetiologies may occur in combination, e.g. patients with myocarditis may have excessive alcohol intake or pathogenic mutations. This is likely to aggravate the resulting DCM phenotype. Thus a patient with genetic DCM may benefit from removal of any environmental factor that burdens the susceptible myocardium.

Proposed diagnostic criteria

While the existing definition of DCM has served well, it has a number of important limitations. Most notable is the fact that the term encompasses a broad range of genetic and acquired disorders that manifest as a spectrum of electrical and functional abnormalities that change with time. This applies particularly to genetic diseases that have delayed or incomplete cardiac expression, with the result that many mutation carriers have intermediate phenotypes that do not meet standard disease definitions.[8,34] Similarly, systolic LV dysfunction or dilatation in acquired diseases such as myocarditis

Table 1 Aetiologies of dilated cardiomyopathy

Group	Subtype disease or agent	Comments
Genetics		
Main genes associated with predominant cardiac phenotype:		
	Titin (TTN)	~20–25% of familial DCM; autosomal-dominant (AD) mode
	Lamin A/C (LMNA)	~6%; AD mode; associated with AVB and VA; can also cause Limb-Girdle myopathy
	Myosin heavy chain (MYH7)	~4%; AD mode
	Troponin T (TNNT2)	~2%; AD mode
	Myosin-binding protein C (MYBPC3)	~2%; AD mode
	RNA-binding Motif-20 (RBM20)	~2%; AD mode
	Myopalladin (MYPN)	~2%; AD mode
	Sodium channel alpha unit (SCN5A)	~2%; AD mode
	BaCl2-associated athanogene 3 (BAG3)	~2%; AD mode
	Phospholamban (PLN)	~1%; AD mode; low QRS voltage on ECG
Neuromuscular disorders		
	Duchenne muscular dystrophy (DMD)	X-linked mode; CK elevation; paediatric patients
	Becker muscular dystrophy (BMD)	X-linked mode; CK elevation; paediatric or adult patients
	Myotonic dystrophy or Steinert (MD)	AD mode; AV block
Syndromic diseases		
	Mitochondrial diseases	Mitochondrial inheritance syndromic expression including skeletal myopathy
	Tafazin (TAZ/G4.5)	X-linked mode; paediatric patients; Barth syndrome
Drugs		
	Antineoplastic drugs	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	Chloroquine; all-trans retinoic acid; antiretroviral agents; phenothiazines
Toxic and overload		
	Ethanol	Risk proportional to entity and duration of alcohol intake. Frequent good response after withdrawal
	Cocaine, amphetamines, ecstasy	Chronic users
	Other toxic	Arsenic; cobalt; anabolic/androgenic steroids
	Iron overload	Transfusions; haemochromatosis
Nutritional deficiency		
	Selenium deficiency	Rare, high frequency in some regions in China (Keshan disease)
	Thiamine deficiency (Beri-Beri)	Favoured by malnutrition, alcohol abuse. High-output dilated cardiac failure
	Zinc and copper deficiency	Possible contributors to DCM
	Carnitine deficiency	Paediatric patients
Electrolyte disturbance		
	Hypocalcemia, hypophosphatemia	
Endocrinology		
	Hypo- and hyper-thyroidism	
	Cushing/addison disease	
	Phaeocromocytoma	
	Acromegaly	
	Diabetes mellitus	

Continued

Table 1 *Continued*

Group	Subtype disease or agent	Comments
Infection		
	Viral (including HIV), bacterial (including Lyme disease), mycobacterial, fungal, parasitic (Chagas disease)	DCM caused by infectious myocarditis. Atrio-ventricular block (AVB) in Lyme disease. Chagas' disease: DCM develops after a long latent infection
Auto-immune diseases		
Organspecific		
	Giant-cell myocarditis (GCM)	Multinucleated giant cell; frequent AV block and ventricular arrhythmia
	Inflammatory DCM	DCM caused by biopsy-proven, non-infectious myocarditis
Not organ specific		
	Polymyositis/dermatomyositis; Churg–Strauss syndrome; Wegener's granulomatosis; systemic lupus erythematosus, sarcoidosis	In cardiac sarcoidosis there is granulomatous myocarditis; AV block is frequent DCM is possible but uncommon in these diseases
Peripartum		Risk factors: multiparity, African descent, familial DCM, autoimmunity

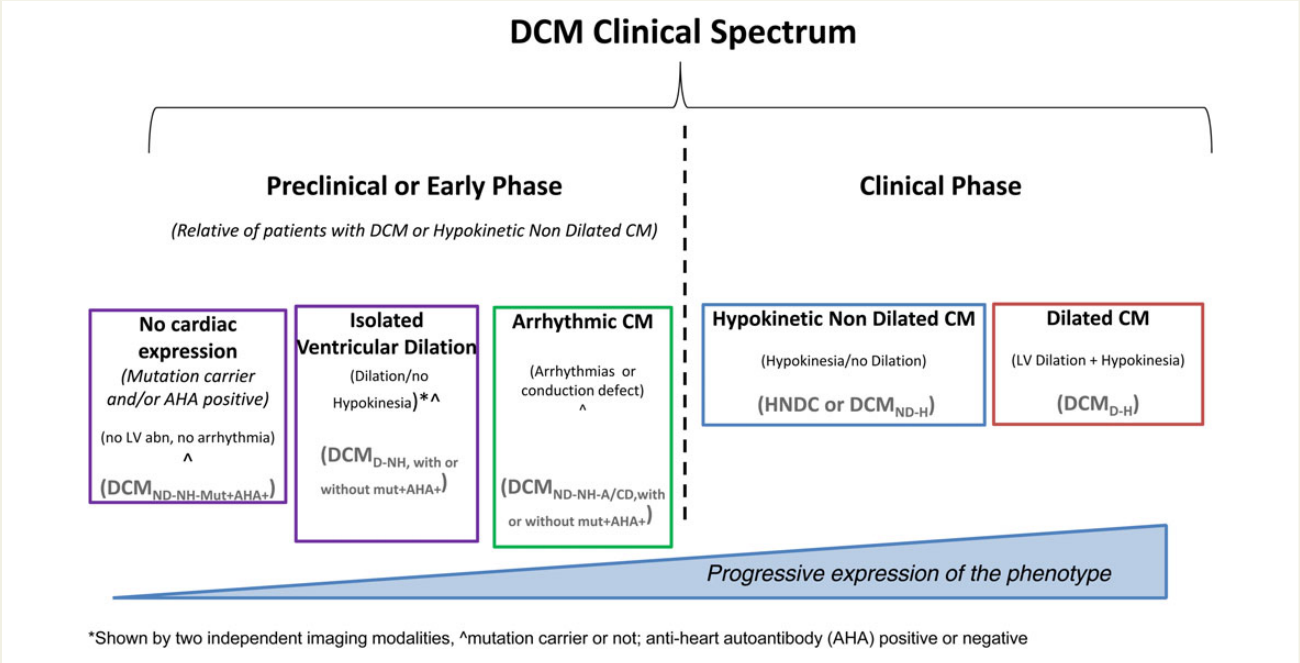

Figure 1 Description of the clinical spectrum of DCM. LV abn, left ventricle abnormality. DCM can be further classified as ND or D (non-dilation/dilation) or NH or H (non-hypokinetic/hypokinetic) or mut+ (mutation carrier) or AHA+ (anti-heart autoantibody positive) or A/CD (arrhythmia/conduction defect).

can be very mild or in some circumstances absent in spite of the presence of clinically significant myocardial disease on cardiac MRI, radionuclide studies or EMB.[3,35] For these reasons, we believe that clinical diagnosis and ultimately treatment can be improved by updating the criteria for diagnosis in relatives of DCM patients and the creation of a new category of *hypokinetic non-dilated cardiomyopathy (HNDC)*.

The clinical spectrum of DCM is described in *Figure 1*. In many individuals—for example, relatives who are mutation carriers or exhibit anti-heart antibodies—there is a preclinical phase without cardiac expression that subsequently progresses towards mild cardiac abnormalities, such as isolated LV dilatation (present in ~25% of relatives of familial DCM and which predicts development of a full phenotype during following years),[9–11] or arrhythmogenic features

(ventricular or supra-ventricular arrhythmia or conduction defects) that can be observed in myocarditis[3,36] or in the early phase of genetic diseases such as lamin A/C and neuromuscular disorders.[15] The overt phase of systolic dysfunction is usually associated with LV dilatation, but this may be absent in some cases causing diagnostic confusion (described in Lamin A/C gene mutation carriers[37,38] and also in some patients without a known genetic cause[13]). For this reason we propose a new category of *HNDC*.

Definitions

Dilated cardiomyopathy

Left ventricular or biventricular systolic dysfunction and dilatation that are not explained by abnormal loading conditions or coronary artery disease.

Notes:

Systolic dysfunction is defined by abnormal LV ejection fraction,[20] measured using any modality and shown either by two independent imaging modalities or on two distinct occasions by the same technique, preferably echocardiograohy or CMR.[20]

Left ventricular dilatation is defined by LV end-diastolic (ED) volumes or diameters >2SD from normal according to normograms (Z scores >2 standard deviations) corrected by body surface area (BSA) and age, or BSA and gender. Normograms for echocardiographic volumes and diameters are available for adults and children[39] and can be calculated using web-based calculators (www.parameterz.com) and by an App (ParameterZ an for iPhone/ipad platform).[40]

Hypokinetic non-dilated cardiomyopathy

Left ventricular or biventricular global systolic dysfunction without dilatation (defined as LVEF < 45%), not explained by abnormal loading conditions or coronary artery disease.

Note:

Strictly decreased LVEF is mandatory in index patient with HNDC since no combination with dilatation is mandatory for the diagnosis.

Diagnostic criteria in relatives

As the relatives of patients with DCM or with HNDC can develop overt disease, they should be considered for clinical and genetic screening.[8,34] However, clinical testing in relatives often reveals mild non-diagnostic abnormalities that overlap with normal variation or mimic changes seen in other more common diseases such as hypertension and obesity. In this statement, we propose three new diagnostic categories for relatives of cases with either DCM or HNDC who undergo screening, which takes into account whether a definite causative mutation has been identified as well as the presence of clinical features that are associated with the development of overt DCM (major criteria) or are suggestive of incomplete disease expression (minor criteria). We acknowledge that evidence to support the use of minor criteria in this context is based on small studies or DCM caused by specific mutations.[30]

By using genotype to lower the diagnostic threshold, but not to characterize the phenotypic status *per se*, we also acknowledge genotype as a static, continuously present susceptibility factor that differs from more dynamic phenotypic expressions.

Recommendation 1: Definition of disease in a relative (briefly summarized in *Figure 3*)

Definite disease

Meets criteria for DCM or HNDC

Probable disease

When:

(i) One major criterion (from Box 1) plus at least one minor criterion (from Box 1)
OR
(ii) One major criterion (from Box 1) plus carrying the causative mutation identified in the proband

Possible disease

When:

(i) Two minor criteria (from Box 1)
OR
(ii) One minor criterion (from Box 1) plus carrying the causative mutation identified in the proband
(iii) One major criterion (from Box 1) but without any minor criterion and without genetic data within the family

Recommendation 2: Definition of familial disease

Definition of familial disease in the absence of conclusive molecular genetic information in a family:

(1) When two or more individuals (first or second degree relatives) have DCM or HNDC fulfilling diagnostic criteria for 'definite' disease
OR
(2) In the presence of an index patient fulfilling diagnostic criteria for DCM/HNDC and a first-degree relative with autopsy-proven DCM and sudden death[1] at <50 years of age

Box 1 Diagnostic criteria for relatives

MAJOR

1. Unexplained decrease of LVEF ≤50% but >45%
   OR
2. Unexplained LVED dilatation (diameter or volume) according to nomograms (*LVED diameter/volume >2SD + 5% since this more specific echocardiographic criterion was used in studies that demonstrated the predictive impact of isolated dilatation in relatives*)[a]

MINOR

1. Complete LBBB, or AV block (PR >200 ms or higher degree AV block)
2. Unexplained ventricular arrhythmia (>100 ventricular premature beats per hour in 24 h or non-sustained ventricular tachycardia, ≥3 beats at a rate of ≥120 beats per minute).
3. Segmental wall motion abnormalities in the left ventricle in the absence of intraventricular conduction defect
4. Late enhancement (LGE) of non-ischaemic origin on cardiac magnetic resonance imaging.
5. Evidence of non-ischaemic myocardial abnormalities (inflammation, necrosis and/or fibrosis) on EMB.
6. Presence of serum organ-specific and disease-specific AHA by one or more autoantibody tests.

Note: [a]Feature shown either by two independent imaging modalities or on two distinct occasions by the same technique

Overlap with arrhythmogenic right ventricular cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) or arrhythmogenic cardiomyopathy (AVC) is a progressive heart muscle disorder defined by replacement of cardiomyocytes by fat and fibrosis that is associated with structural and functional abnormalities of the right ventricle (RV). It is usually inherited as an autosomal-dominant trait caused by mutations in genes encoding for desmosomal proteins, although a number of other genetic and non-genetic phenocopies (e.g. myocarditis) are recognized. While RV disease defines the condition, there are a number of features that can overlap with DCM as defined in this statement. In particular, LV involvement ranging from scars on CMR to severe LV dilation and systolic impairment which has been reported in up to 76% of patients. There is also overlap in causation—for example, desmosomal gene mutations are relatively common in patients with a clinical diagnosis of DCM.[17] Although the degree to which both DCM and ARVC coexist within families is poorly characterized, the presence of right ventricular abnormalities such as dilatation and ventricular ectopy of right ventricular origin in relatives of patients with DCM may be a diagnostic red flag for the presence of familial disease.[35] Similarly, the presence of LV dysfunction in a relative of a patient with unequivocal ARVC does not necessarily imply a different disease. Myocarditis with or without a DCM phenotype may mimic ARVC and EMB may be required for differential diagnosis.[35]

Diagnostic work-up in index patients

Considering the broad spectrum of disorders that cause DCM, a systematic approach can be helpful (*Figure 2*) in identifying and managing uncommon but clinically important forms of DCM. The principles of this process are described elsewhere in another position statement from this Working Group.[8] In brief, the systematic search for diagnostic clues or 'red flags' can suggest particular disorders and guide rational selection of additional diagnostic tests. Importantly, each stage of the clinical pathway from history to molecular testing has value.

Some of the most important diagnostic clues are described in Supplementary material online, *Table S2*. Clinical workup starts with personal and family history, physical examination, and a focused analysis of ECG and echocardiography (*Figure 2*). Identification of clinical features suggestive of specific diseases should then lead to a second-level diagnostic work-up that may include biochemical analyses, MRI, EMB, and genetic testing. Diagnostic work-up should take into account the age of the patient (see Supplementary material online, *Figure S1*).

The role of genetic testing in cardiomyopathies has been the subject of a previous position Statement of this Working Group.[34] Once a mutation is identified, and its pathogenic role is established, then this may have multiple impacts since the information is able to confirm the genetic origin and mode of inheritance, may be used for guidance of therapy and can be used for family cascade screening and early diagnosis.

Recommendation 3: **Diagnostic work-up**

(1) Coronary artery disease should be excluded in patients more than 35 years of age, or before 35 years if there are significant personal coronary artery disease (CAD) risk factors or a family history of early CAD.

(2) First-line laboratory testing should include creatine kinase (CK), renal function, urine analysis for proteinuria, liver function tests, haemoglobin and white blood cell count, serum iron, ferritin, calcium, phosphate, natriuretic peptides and thyroid stimulating hormone.

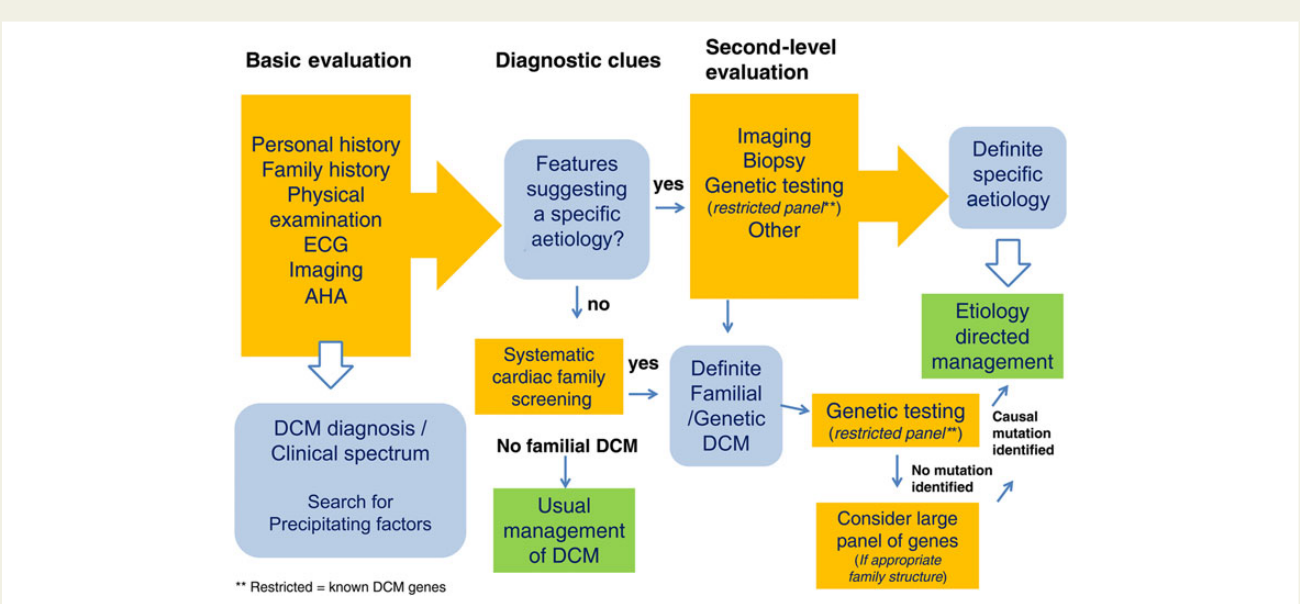

Figure 2 Diagnostic work-up for aetiology assessment.

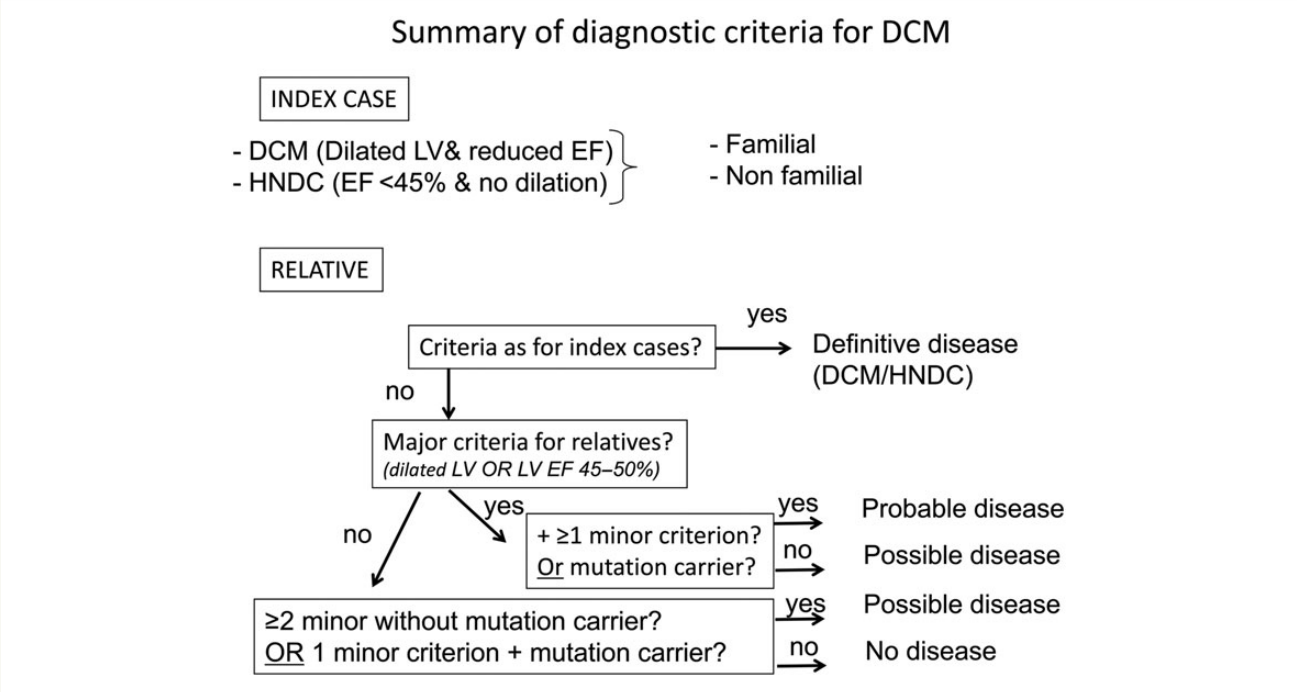

Figure 3 Overview of dilated cardiomyopathy criteria in probands and relatives.

(3) Second-line diagnostics should be targeted to the suspected aetiology.
(4) Cardiac magnetic resonance (CMR) may be useful for assessment of ventricular size and function and for tissue characterization.[3]
(5) In patients with clinically suspected myocarditis[3] (EMB [including histology, immunohistology, and polymerase chain reaction (PCR)] for infectious agents is recommended. Endomyocardial biopsy should also be considered when there is clinical suspicion of storage or metabolic diseases that cannot be confirmed by other means.
(6) Cardiac screening with echocardiography and ECG is recommended in all first degree-relatives of an index patient with DCM, irrespective of family history.
(7) Genetic testing is recommended in the presence of a familial form of DCM OR in sporadic DCM with clinical clues suggestive of a particular/rare genetic disease (such as atrio-ventricular block or CK elevation).
(8) Genetic testing should be oriented by clinical diagnostic clues when present, and should be restricted to genes known to cause DCM. The use of next-generation sequencing (NGS) for the analysis of very large panels of genes, including titin, may be considered when the family structure permits segregation analysis (i.e. several patients with DCM and DNA available).

Aetiology-directed management and therapy

The identification of a specific underlying cause for DCM can have profound consequences for clinical management. For example, identification of a definite genetic cause should lead to genetic counselling and screening of relatives and in some specific circumstances prompt regular monitoring for complications such as conduction disease. It also has significant consequences for advice on contraception and reproduction (see Supplementary material online, *Table S3*) and in a number of examples, early intervention with ICDs, lifestyle modification, and specific drug therapy may also be necessary. General advice on the management of heart failure can be found in current ESC guidelines for chronic heart failure.[20] In DCM caused by LMNA mutations, risk assessment also involves gender-specific risk as described elsewhere.[41]

Relatives with minor cardiac abnormalities such as LV enlargement are at increased risk of DCM development[11] and may benefit from early medical treatment (although this has not yet demonstrated by placebo controlled trials).[42] We provide a summary of advice for the management of pregnancy in Supplementary material online, *Table 3A* and *B*.

Familial dilated cardiomyopathy and follow-up of relatives

Recommendation 4

- In the context of familial DCM, cardiac screening with Echo and ECG ($\pm$ Holter monitoring depending upon main phenotype in proband) should be performed in all first degree-relatives (from childhood) and should be repeated every 2–3 years if cardiovascular tests are normal, every year if minor abnormalities are detected, whenever symptoms develop. Search in a relative for conduction defects or arrhythmia which may be an early

presentation of DCM, especially in the context of an LMNA gene mutation.

Recommendation 5

- When a causative mutation has been identified in a DCM patient, then predictive genetic testing should be offered to first-degree relatives in order to guide cardiac follow-up.

Recommendation 6

- When a definite causative LMNA mutation is identified, early indication for primary prevention by ICD implantation should be considered (guided by the risk factors as detailed elsewhere).[43,44]

Inflammatory dilated cardiomyopathy

Recommendation 7

- In familial and non-familial pedigrees with biopsy-proven inflammatory DCM in the index case, cardiac-specific autoantibody (AHA) test at baseline and at follow-up should be considered in symptom-free relatives with or without cardiac abnormalities (e.g. ECG, echocardiography, CMR).
- Non-invasive cardiac screening with echocardiography and ECG may be more frequent in relatives with cardiac autoantibodies.
- Immunomodulatory and/or immunosuppressive therapy in biopsy-proven non-infectious inflammatory DCM should be considered.
- Physical activity should be restricted in DCM with underlying biopsy-proven active phase of myocarditis.

Summary

In this paper the Working Group on Myocardial and Pericardial Disease proposes a revised definition of DCM (see also *Figure 3*) in an attempt to bridge the gap between our recent understanding of the disease spectrum and its clinical presentation in relatives, which is key for early diagnosis and the institution of potential preventative measures. We also provide practical hints to identify subsets of the DCM syndrome where aetiology-directed management has great clinical relevance.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Authors' contributions

Y.P., P.C., A.C., and P.E. conceived and designed the research. All co-authors have been involved in writing the manuscript and made critical revision for key intellectual content.

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Conflict of interest: Y.M.P. has stock in University biomedical spin-off on biomarkers and received consulting/speaker fees from Roche Diagnostics, Novartis, and MyoKardia. P.E. received consulting and speaker fees for Genzyme, Shire, Pfizer, and Amicus. S.S. is working as a proctor for HeartWare International. A.L. received speaker's honoraria and consulting fees from Shire HGT, Genzyme a sanofi comp., Amicus Therpautics, Actelion Pharmaceuticals, and Boehringer Ingelheim. D.D. is on advisory board at Novartis, Amgen, Genzyme, Janssen, GSK, and Daichii-Sankyo and also on advisory board and an SMB member at EspeRare Foundation. M.B. is on advisory board at Servier, Novartis.

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