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ESC WORKING GROUP ON MYOCARDIAL AND PERICARDIAL DISEASES: KEY MESSAGES on Dilated Cardiomyopathy

(original title: Proposal for a Revised Definition of Dilated Cardiomyopathy, Hypokinetic Non-Dilated Cardiomyopathy, and its Implications for Clinical Practice: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J. 2016 Jan 19. pii: ehv727. [Epub ahead of print]

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1. Introduction and scope of the document

Research over recent decades has shed new light on the aetiology and natural history of dilated cardiomyopathy (DCM). 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.

It is also clear that distinct subtypes in fact share a common DCM phenotype. The aim of this position paper is to update the definition of DCM to take into account its diverse aetiology and clinical 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 but do consider the implications of an aetiology oriented approach to therapy.

2. Basic definition and Causes

DCM 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.

The causes of DCM can be classified as genetic or non-genetic (**Table 1**), but there are circumstances in which genetic predisposition interacts with extrinsic or environmental factors.

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

Table 1 Aetiologies of dilated cardiomyopathy (continued)		
Group	**Subtype disease or agent**	**Comments**
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	

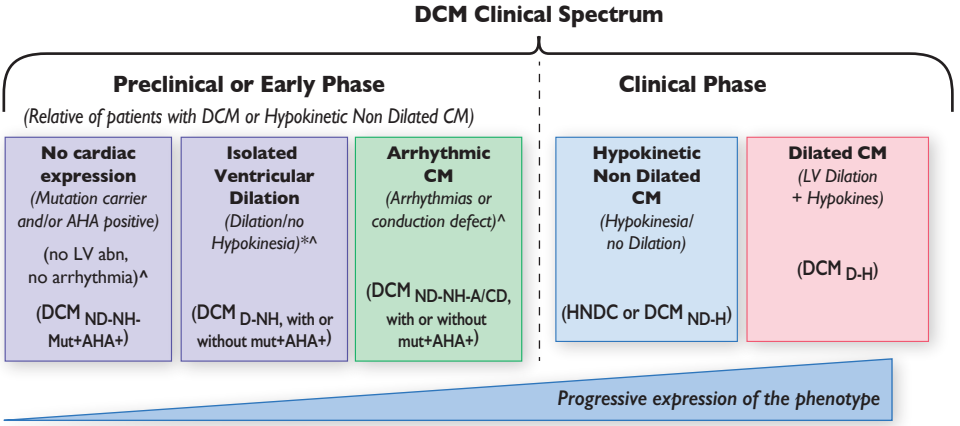
Table 1 Aetiologies of dilated cardiomyopathy (continued)		
Group	**Subtype disease or agent**	**Comments**
Infection	Viral (including HIV), bacterial (including Lyme disease), mycobacterial, fungal, parasitic (Chagas disease)	DCM caused by infectious myocarditis. Atrio-ventricular block (AVB) in Lyme disease. Chagas' disease: DCM develops after a long latent infection.
Auto-immune diseases		
Organ specific	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

3. Refined definitions and diagnostic criteria

Existing definition of DCM 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. Similarly, systolic LV dysfunction or dilatation in acquired diseases such as myocarditis 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 endomyocardial biopsy. 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. The clinical spectrum of DCM is described in Figure 1.

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).



* Shown by two independent imaging modalities - ^mutation carrier or not; anti-heart autoantibody (AHA) positive or negative

3.1 Dilated Cardiomyopathy (DCM)

Definition: 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 , 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. LV 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 and can be calculated using web-based calculators (www.parameterz.com) and by an App (ParameterZan for iPhone/ipad platform).

3.2 Hypokinetic non-dilated cardiomyopathy (HNDC)

Definition: 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.*

3.3 Diagnostic criteria in relatives

As the relatives of patients with DCM or with hypokinetic non-dilated cardiomyopathy (HNDC) can develop overt disease, they should be considered for clinical and genetic screening. 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.

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 (W100 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.

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

Recommendation 1: Definition of disease in a relative

- **Definite Disease** when:
  Meets criteria for DCM or hypokinetic non-dilated cardiomyopathy (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
  OR
  (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 *(in the absence of conclusive molecular genetic information in a family)**:***

1. *When two or more individuals (1st or 2nd 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.*

4. Diagnostic work-up

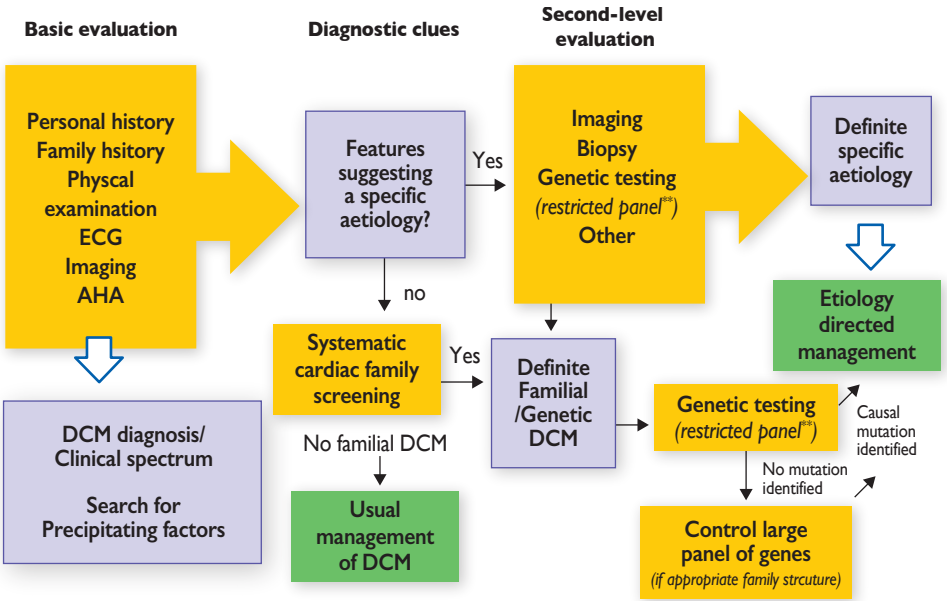
4.1 General process

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. In brief, the systematic search for diagnostic clues or "red flags" can suggest particular disorders and guide rational selection of additional diagnostic tests. Clinical workup starts with personal and family history, physical examination, and a focused analysis of ECG and echocardiography (**figure 2**).

Some of the most important diagnostic clues are described in **table 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, endomyocardial biopsy and genetic testing. The role of genetic testing in cardiomyopathies has been the subject of a previous Position Statement of this Working Group.

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.

Figure 2 Diagnostic work-up for aetiology assessment.

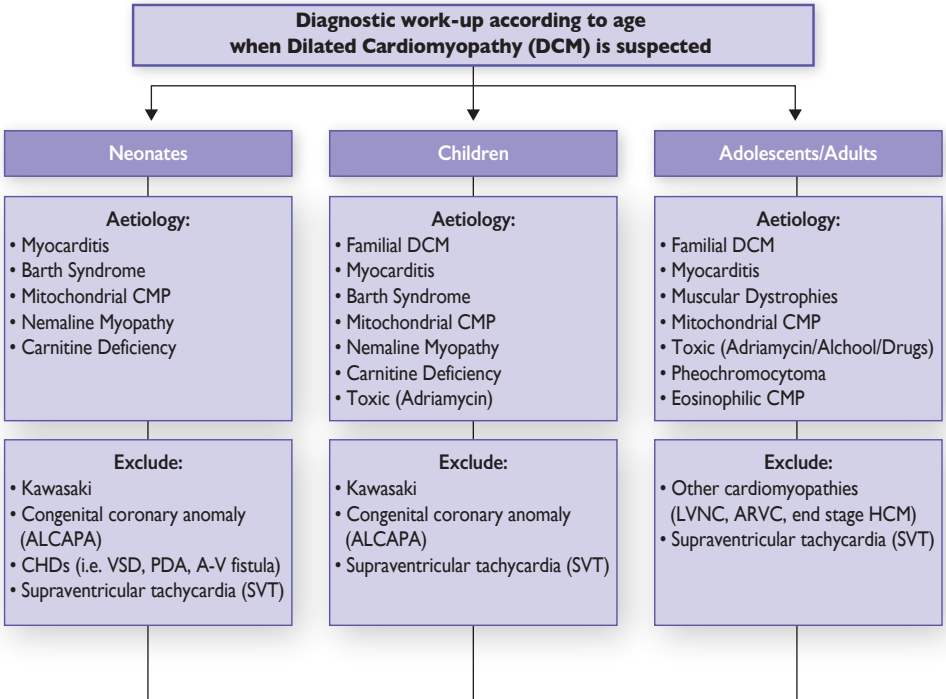


** Restricted = known DCM genes

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.*
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*
5. *In patients with clinically suspected myocarditis, endomyocardial biopsy (EMB) (including histology, immunohistology and polymerase chain reaction (PCR) for infectious agents is recommended. EMB 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).*

4.2 Diagnostic work-up according to age



Work-up:

- Imaging: CHDs, coronary arteries origin, aortic istmus morpholgy/Doppler flow
- Biochemical: Blood (full blood count, glucose, CK, thyroid hormones, lactate, pyruvate, carnitine, respiratory chain analysis), Urine (organic acids including 3-methylglutaconic acid)
- Genetics: mitochondrial genome
- Muscle biopsy and EMB (histology, immunohistology, viral genome PCR)

Work-up:
As neonates.
Add also:
sarcomeric gene analysis

Work-up:
As neonates and children.
Add also:
urine cathecholamines

4.3 Diagnostic work-up according to red flags

The most important clues for an appropriate diagnosis of the underlying etiology are described below.

Table 2A: Examples of signs and symptoms that raise the suspicion of specific aetiologies

Finding	DCM
Intellectual disability	Dystrophinopathies • Mitochondrial diseases • Myotonicdystrophy FKTN mutations
Sensorineuraldeafness	Epicardin mutation • Mitochondrial diseases
Visual impairment	CRYAB (polar cataract) • Type 2 myotonic dystrophy (subcapsular cataract)
Gaitdisturbance	Dystrophinopathies • Sarcoglycanopathies • Myofibrillar myopathies
Myotonia (involuntary muscle contraction with delayed relaxation)	Myotonic dystrophy (type I and Type 2)
Muscle weakness	Dystrophinopathies • Sarcoglycanopathies • Laminopathies • MyotonicDystrophy Desminopathy
Palpebral ptosis	Mitochondrial disease
Pigmentation of skin and scars	Haemochromatosis
Palmoplantarkeratoderma and woolly hair	Carvajal syndrome

Table 2B Electrocardiographic abnormalities that suggest specific diagnoses	
Finding	**Specific diseases to be considered**
A-V block	Laminopathy • Emery Dreifuss 1 • Myocarditis • Sarcoidosis • Desminopathy Myotonicdystrophy
Low P wave amplitude	Emery Dreifuss 1 & 2
Atrial standstill	Emery Dreifuss 1 & 2
"Posterolateral infarction"	Dystrophin-related cardiomyopathy • Limb-girdle muscular dystrophy • Sarcoidosis
Low QRS voltage + "atypical RBBB"	ARVC with biventricular involvement
Extremely low QRS amplitude	PLN mutation

Table 2C Abnormalities in routine laboratory tests that can raise the suspicion of specific cardiomyopathies	
Finding	**DCM**
↑ Creatine kinase	Dystrophinopathies Sarcoglycanopathies • Zaspopathies (LDB3gene) • Laminopathies Myotonicdystrophy • FKTN mutations • Desminopathies • Myofibrillar myopathies
High transferrin saturation / hyperferritinaemia	Haemochromatosis
Lacticacidosis	Mitochondrial diseases
Myoglobinuria	Mitochondrial diseases
Leucocytopenia	Mitochondrial diseases (TAZ gene/ Barth Syndrome)

SUPPL Table 2D Echocardiographic clues to diagnosis in DCM	
Finding	**Specific diseases to be considered**
LV noncompaction	Genetic DCM (G4.5, ZASP, sarcomeric mutations)
Postero-lateralakinesia/dyskinesia	Dystrophin-related cardiomyopathy
Mild (absent) dilatation +akinetic/dyskinetic segments with noncoronary distribution	Myocarditis • Sarcoidosis

SUPPL Table 2E Cardiac Magnetic Resonance Imaging: Main hints to orient an aetiological diagnosis	
Hint	**Condition to be suspected**
Short T2 *	Haemochromatosis
Patchy, midwall late gadolinium hyperenhancement (LGE)	Post myocarditis Dystrophinopathy
Akinesia/Dyskinesia + LGE at the anterobasal septum or papillary muscles	Sarcoidosis
Fatty replacement (T1w FS) within LV wall	ARVC "Left Dominant"

5. Etiology 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 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. In DCM caused by LMNA mutations, risk assessment also involves gender-specific risk as described elsewhere. Relatives with minor cardiac abnormalities such as LV enlargement are at increased risk of DCM development and may benefit from early medical treatment (although this has not yet demonstrated by placebo controlled trials).

5.1 Familial DCM and follow up of relatives

Recommendation 4:

- *In the context of familial DCM, cardiac screening with Echo and ECG (± Holter* monitoring depending on 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 ar arrhythmia which may be an early representation of DCM, especially in the context of a 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).*

5.2 Inflammatory DCM

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.*

6. Pregnancy counseling

We provide a summary of advice for the management of pregnancy in women with DCM in **Tables 3 & 4**.

Table 3 Pregnancy counseling, risk assessment and management

Pregnancy risk and management*	
Counselling	Girls and women of fertile age should receive counseling concerning contraceptives, pregnancy risk, and the risk of genetic transmission. (Regitz 2011).
Risk assessment	• Increased risk of heart failure, arrhythmias, thrombo-embolic events (39%) (Grewal 2010) • Predictors of increased risk: NYHA class III/IV, LVEF < 45% • Pregnancy contra-indicated: NYHA III/IV, LVEF < 30% • Risk of offspring events (low birth weight, premature delivery)

Table 3 Pregnancy counseling, risk assessment and management (continued)	
Pregnancy risk and management*	
Delivery	• Usually vaginal delivery with epidural anesthesia • Caesarean section: for obstetric indication and unstable heart failure • Observation period postpartum: 48-72 hours because of increased risk of heart failure peripartum

Table 4 Contraceptives and medication during pregnancy in women with DCM	
Medication during pregnancy	
ACE inhibitors and angiotensin receptor blockers	Contraindicated during whole pregnancy because of fetotoxicity. Skull and lung hypoplasia, renal failure, anuria, fetal death, limb and craniofacial deformations. Breastfeeding: captopril and enalapril: low dose in breast milk but breast feeding not advised. Others do not use.
Anticoagulants	
Vitamin K antagonists	Embryopathy when used in first trimester, dose dependant. Vaginal delivery contra-indicated because of risk of intracranial bleeding.
Low molecular weight heparin	Preferred in first trimester and last month of pregnancy. Dose adjustment according to weight and anti factor X-a levels
Dabigatran, rivaroxaban	Do not use during pregnancy and breast-feeding
Beta-blockers	• Low birthweight, neonatal bradycardia and hypoglycaemia. • Preferred beta-blockers during pregnancy and breast feeding are metoprolol and labetalol. Do not use atenolol.
Diuretics	Risk of oligohydramnion and electrolyte disbalance in fetus. No fetotoxicity. Breast feeding: hydrochlorothizide preferred over furosemide, do not use bumetanide.

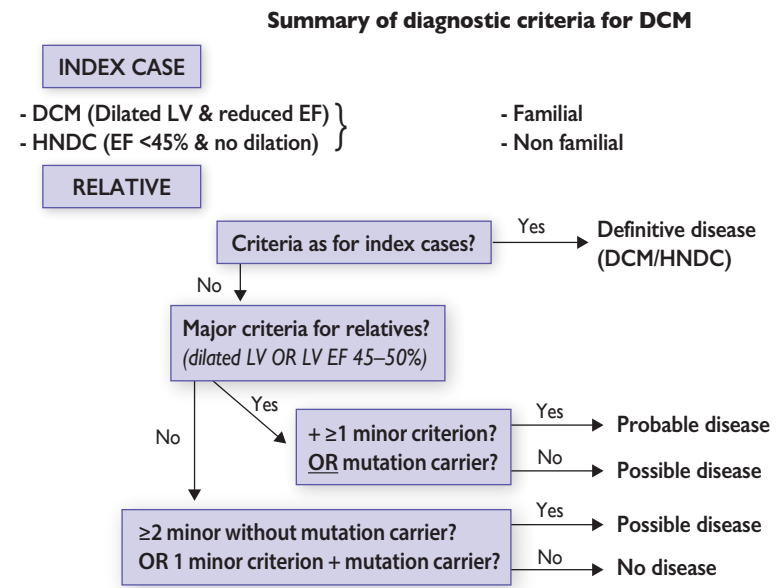
Table 4 Contraceptives and medication during pregnancy in women with DCM (continued)	
Medication during pregnancy	
Aldosterone antagonists	Antiandrogenic effects and endocrine dysfunction. Only use when no other alternative. Do not use when breastfeeding.
Anti-arrhythmic drugs	• Amiodarone: Fetotoxic. Do only use with severe arrhythmias when no other alternative is available. High dose in breast milk, do not use • Flecainide: Limited data, may be used with caution. • Procainamide: Limited data, use only when necessary. • Sotalol: Possibly bradycardia and hypoglycaemia in neonate. No harm in animal studies. May be used with caution.
Other drugs	
Digoxin	• Probably not harmful during pregnancy and breastfeeding
Ivabradin	• Contra-indicated during pregnancy

7. Summary

In this paper the Working Group on Myocardial and Pericardial Diseases proposes a revised definition of 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.

We have below summarized in **figure 3** the diagnostic tree that emerges from the novel classification of DCM.

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



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