Special thanks to

Shire
Genzyme

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


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

**DCM Clinical Spectrum**

### Preclinical or Early Phase
(Relative of patients with DCM or Hypokinetic Non Dilated CM)

- **No cardiac expression**
  - (Mutation carrier and/or AHA positive)
  - (no LV abn, no arrhythmia)^
  - (DCM ND-NH-Mut+AHA+)

- **Isolated Ventricular Dilation**
  - (Dilation/no Hypokinesia)*^
  - (DCM D-NH, with or without mut+AHA+)

- **Arrhythmic CM**
  - (Arrhythmias or conduction defect)^
  - (DCM ND-NH-A/CD, with or without mut+AHA+)

### Clinical Phase

- **Hypokinetic Non Dilated CM**
  - (Hypokinesia/no Dilation)
  - (HNDC or DCM ND-H)

- **Dilated CM**
  - (LV Dilation + Hypokines)
  - (DCM D-H)

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* 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 echocardiography 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**

<table>
<thead>
<tr>
<th><strong>MAJOR</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Unexplained decrease of LVEF ≤50% but &gt;45%</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>2. Unexplained LVED dilatation (diameter or volume) according to nomograms (LVED diameter/volume &gt;2SD + 5% since this more specific echocardiographic criterion was used in studies that demonstrated the predictive impact of isolated dilatation in relatives)*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>MINOR</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Complete LBBB, or AV block (PR &gt;200 ms or higher degree AV block)</td>
</tr>
<tr>
<td>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).</td>
</tr>
<tr>
<td>3. Segmental wall motion abnormalities in the left ventricle in the absence of intraventricular conduction defect</td>
</tr>
<tr>
<td>4. Late enhancement (LGE) of non-ischaemic origin on cardiac magnetic resonance imaging.</td>
</tr>
<tr>
<td>5. Evidence of non-ischaemic myocardial abnormalities (inflammation, necrosis and/or fibrosis) on EMB.</td>
</tr>
<tr>
<td>6. Presence of serum organ-specific and disease-specific AHA by one or more autoantibody tests.</td>
</tr>
</tbody>
</table>

*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:
  1. One major criterion (from Box 1) plus at least one minor criterion (from Box 1) OR
  2. One major criterion (from Box 1) plus carrying the causative mutation identified in the proband

- **Possible disease** when:
  1. Two minor criteria (from Box 1) OR
  2. One minor criterion (from Box 1) plus carrying the causative mutation identified in the proband OR
  3. 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.

Basic evaluation
- Personal history
  - Family history
  - Physical examination
  - ECG
  - Imaging
  - AHA
- DCM diagnosis/Clinal spectrum
- Search for Precipitating factors

Diagnostic clues
- Features suggesting a specific aetiology?
  - Yes
  - Imaging
    - Biopsy
    - Genetic testing (restricted panel**)
    - Other
  - No
- Systematic cardiac family screening
  - Yes
  - Definite Familial/Genetic DCM
  - No familial DCM
    - Usual management of DCM
    - Genetic testing (restricted panel**)
      - Control large panel of genes (if appropriate family structure)
      - Causal mutation identified
      - No mutation identified

Second-level evaluation
- Definite specific aetiology
- Etiology directed management

** 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

**Diagnostic work-up according to age when Dilated Cardiomyopathy (DCM) is suspected**

- **Neonates**
  - **Aetiology:**
    - Familial DCM
    - Myocarditis
    - Barth Syndrome
    - Mitochondrial CMP
    - Nemaline Myopathy
    - Carnitine Deficiency
  - **Exclude:**
    - Kawasaki
    - Congenital coronary anomaly (ALCAPA)
    - CHDs (i.e. VSD, PDA, A-V fistula)
    - Supraventricular tachycardia (SVT)

- **Children**
  - **Aetiology:**
    - Familial DCM
    - Myocarditis
    - Barth Syndrome
    - Mitochondrial CMP
    - Nemaline Myopathy
    - Carnitine Deficiency
    - Toxic (Adriamycin)
  - **Exclude:**
    - Kawasaki
    - Congenital coronary anomaly (ALCAPA)
    - CHDs (i.e. VSD, PDA, A-V fistula)
    - Supraventricular tachycardia (SVT)

- **Adolescents/Adults**
  - **Aetiology:**
    - Familial DCM
    - Myocarditis
    - Muscular Dystrophies
    - Mitochondrial CMP
    - Toxic (Adriamycin/Alcohol/Drugs)
    - Pheochromocytoma
    - Eosinophilic CMP
  - **Exclude:**
    - Other cardiomyopathies (LVNC, ARVC, end stage HCM)
    - Supraventricular tachycardia (SVT)
### Diagnostic work-up according to age when Dilated Cardiomyopathy (DCM) is suspected

#### Children

**Aetiology:**
- Familial DCM
- Myocarditis
- Barth Syndrome
- Mitochondrial CMP
- Nemaline Myopathy
- Carnitine Deficiency
- Toxic (Adriamycin)

**Exclude:**
- Kawasaki
- Congenital coronary anomaly (ALCAPA)
- Supraventricular tachycardia (SVT)

**Work-up:**
- Imaging: CHDs, coronary arteries origin, aortic istmus morphology/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)

#### Adolescents/Adults

**Aetiology:**
- Myocarditis
- Barth Syndrome
- Mitochondrial CMP
- Nemaline Myopathy
- Carnitine Deficiency
- Toxic (Adriamycin, Alcohol, Drugs)
- Pheochromocytoma
- Eosinophilic CMP

**Exclude:**
- Other cardiomyopathies (LVNC, ARVC, end stage HCM)
- Supraventricular tachycardia (SVT)

**Work-up:**
- As neonates and children.
  - Add also: sarcomeric gene analysis
  - Add also: urine catecholamines
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>
<thead>
<tr>
<th>Finding</th>
<th>DCM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intellectual disability</td>
<td>Dystrophinopathies • Mitochondrial diseases • Myotonic dystrophy • FKTN mutations</td>
</tr>
<tr>
<td>Sensorineural deafness</td>
<td>Epicardin mutation • Mitochondrial diseases</td>
</tr>
<tr>
<td>Visual impairment</td>
<td>CRYAB (polar cataract) • Type 2 myotonic dystrophy (subcapsular cataract)</td>
</tr>
<tr>
<td>Gait disturbance</td>
<td>Dystrophinopathies • Sarcoglycanopathies • Myofibrillar myopathies</td>
</tr>
<tr>
<td>Myotonia (involuntary muscle contraction with delayed relaxation)</td>
<td>Myotonic dystrophy (type 1 and Type 2)</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>Dystrophinopathies • Sarcoglycanopathies • Laminopathies • Myotonic Dystrophy Desminopathy</td>
</tr>
<tr>
<td>Palpebral ptosis</td>
<td>Mitochondrial disease</td>
</tr>
<tr>
<td>Pigmentation of skin and scars</td>
<td>Haemochromatosis</td>
</tr>
<tr>
<td>Palmoplantar keratoderma and woolly hair</td>
<td>Carvajal syndrome</td>
</tr>
</tbody>
</table>
**Table 2B Electrocardiographic abnormalities that suggest specific diagnoses**

<table>
<thead>
<tr>
<th>Finding</th>
<th>Specific diseases to be considered</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-V block</td>
<td>Laminopathy • Emery Dreifuss I &amp; 2 • Myocarditis • Sarcoidosis • Desminopathy Myotonicdystrophy</td>
</tr>
<tr>
<td>Low P wave amplitude</td>
<td>Emery Dreifuss I &amp; 2</td>
</tr>
<tr>
<td>Atrial standstill</td>
<td>Emery Dreifuss I &amp; 2</td>
</tr>
<tr>
<td>“Posterolateral infarction”</td>
<td>Dystrophin-related cardiomyopathy • Limb-girdle muscular dystrophy • Sarcoidosis</td>
</tr>
<tr>
<td>Low QRS voltage + “atypical RBBB”</td>
<td>ARVC with biventricular involvement</td>
</tr>
<tr>
<td>Extremely low QRS amplitude</td>
<td>PLN mutation</td>
</tr>
</tbody>
</table>

**Table 2C Abnormalities in routine laboratory tests that can raise the suspicion of specific cardiomyopathies**

<table>
<thead>
<tr>
<th>Finding</th>
<th>DCM</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ Creatine kinase</td>
<td>Dystrophinopathies Sarcoglycanopathies • Zaspopathies (LDB3gene) • Laminopathies Myotonicdystrophy • FKTN mutations • Desminopathies • Myofibrillar myopathies</td>
</tr>
<tr>
<td>High transferrin saturation / hyperferritinaemia</td>
<td>Haemochromatosis</td>
</tr>
<tr>
<td>Lacticacidosis</td>
<td>Mitochondrial diseases</td>
</tr>
<tr>
<td>Myoglobinuria</td>
<td>Mitochondrial diseases</td>
</tr>
<tr>
<td>Leucocytopenia</td>
<td>Mitochondrial diseases (TAZ gene/ Barth Syndrome)</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>SUPPL Table 2D Echocardiographic clues to diagnosis in DCM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Finding</strong></td>
</tr>
<tr>
<td>LV noncompaction</td>
</tr>
<tr>
<td>Postero-lateralakinesia/dyskinesia</td>
</tr>
<tr>
<td>Mild (absent) dilatation +akinetic/dyskinetic segments with noncoronary distribution</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SUPPL Table 2E Cardiac Magnetic Resonance Imaging: Main hints to orient an aetiological diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hint</strong></td>
</tr>
<tr>
<td>Short T2 *</td>
</tr>
<tr>
<td>Patchy, midwall late gadolinium hyperenhancement (LGE)</td>
</tr>
<tr>
<td>Akinesia/Dyskinesia + LGE at the anterobasal septum or papillary muscles</td>
</tr>
<tr>
<td>Fatty replacement (T1w FS) within LV wall</td>
</tr>
</tbody>
</table>
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 or 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**

<table>
<thead>
<tr>
<th>Pregnancy risk and management*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Counselling</strong></td>
</tr>
<tr>
<td>Girls and women of fertile age should receive counseling concerning contraceptives, pregnancy risk, and the risk of genetic transmission. (Regitz 2011).</td>
</tr>
<tr>
<td><strong>Risk assessment</strong></td>
</tr>
<tr>
<td>• Increased risk of heart failure, arrhythmias, thrombo-embolic events (39%) (Grewal 2010)</td>
</tr>
<tr>
<td>• Predictors of increased risk: NYHA class III/IV, LVEF &lt; 45%</td>
</tr>
<tr>
<td>• Pregnancy contra-indicated: NYHA III/IV, LVEF &lt; 30%</td>
</tr>
<tr>
<td>• Risk of offspring events (low birth weight, premature delivery)</td>
</tr>
<tr>
<td>Table 3 Pregnancy counseling, risk assessment and management (continued)</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Pregnancy risk and management</strong></td>
</tr>
</tbody>
</table>
| **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>
<thead>
<tr>
<th>Table 4 Contraceptives and medication during pregnancy in women with DCM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medication during pregnancy</strong></td>
</tr>
<tr>
<td><strong>Anticoagulants</strong></td>
</tr>
<tr>
<td>Vitamin K antagonists</td>
</tr>
<tr>
<td>Low molecular weight heparin</td>
</tr>
<tr>
<td>Dabigatran, rivaroxaban</td>
</tr>
</tbody>
</table>
| **Beta-blockers** | • Low birthweight, neonatal bradycardia and hypoglycaemia.  
• Preferred beta-blockers during pregnancy and breast feeding are metoprolol and labetalol. Do not use atenolol. |
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.

Table 4 Contraceptives and medication during pregnancy in women with DCM (continued)

<table>
<thead>
<tr>
<th>Medication during pregnancy</th>
<th>Antiandrogenic effects and endocrine dysfunction. Only use when no other alternative. Do not use when breastfeeding.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aldosterone antagonists</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Anti-arrhythmic drugs</strong></td>
<td>• Amiodarone: Fetotoxic. Do only use with severe arrhythmias when no other alternative is available. High dose in breast milk, do not use.</td>
</tr>
<tr>
<td></td>
<td>• Flecainide: Limited data, may be used with caution.</td>
</tr>
<tr>
<td></td>
<td>• Procainamide: Limited data, use only when necessary.</td>
</tr>
<tr>
<td></td>
<td>• Sotalol: Possibly bradycardia and hypoglycaemia in neonate. No harm in animal studies. May be used with caution.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Other drugs</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin</td>
<td>• Probably not harmful during pregnancy and breastfeeding</td>
</tr>
<tr>
<td>Ivabradin</td>
<td>• Contra-indicated during pregnancy</td>
</tr>
</tbody>
</table>
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.

Summary of diagnostic criteria for DCM

INDEX CASE
- DCM (Dilated LV & reduced EF)
- HNDC (EF <45% & no dilation)
- Familial
- Non familial

RELATIVE
Criteria as for index cases?

Yes -> Definitive disease (DCM/HNDC)
No ->

Major criteria for relatives?
(dilated LV OR LV EF 45–50%)

Yes -> Probable disease
No -> Possible disease

+ ≥1 minor criterion? OR mutation carrier?

Yes -> Probable disease
No -> Possible disease

≥2 minor without mutation carrier?
OR 1 minor criterion + mutation carrier?

Yes -> Possible disease
No -> No disease
Authors and Task Force members

Yigal M Pinto¹, Perry M Elliott², Eloisa Arbustini³*, Yehuda Adler⁴, Aris Anastasakis⁵, Michael Bohm⁶*, Denis Duboc⁷, Juan Gimeno⁸, Pascal de Groote⁹, Massimo Imazio¹⁰, Stéphane Heymans¹¹, Karin Klingel¹², Michel Komajda¹³, Giuseppe Limongelli¹⁴, Ales Linhart¹⁵, Jens Mogensen¹⁶, James Moon¹⁷, Petronella G Pieper¹⁸, Petar M Seferovic¹⁹, Stephan Schueler²⁰, José L Zamorano²¹, Alida LP Caforio²², Philippe Charron²³,²⁴.

Author affiliations:

1. Depts 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. Department of Cardiology, Sheba Medical Center, Tel Hashomer, 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, Pôlecardio-vasculaire et Pulmonaire, CHRU de Lille, Lille, France - Inserm U1167, Institut Pasteur de Lille, Université de Lille 2, Lille, France
10. Cardiology Department, Maria Vittoria Hospital and University of Torino, Torino, Italia
11. Cardiovascular Research Institute Maastricht, Department of Cardiology, Maastricht University Medical Center, Netherlands AND: ICIN, Netherlands Heart Institute, Utrecht, Netherlands.
12. Department of Molecular Pathology, Institute for Pathology, University Hospital Tübingen, Germany
14. Division of Cardiology, Monaldi Hospital, Second University of Naples, Naples, Italy
15. Second Department of Medicine, Department of Cardiovascular Medicine, General University Hospital and the First Faculty of Medicine, Charles University, Prague, Czech Republic
16. Department of Cardiology, Odense University Hospital, Odense, Denmark
17. Division of Cardiovascular Imaging and Biostatistics, The Heart Hospital, London, England
18. Department of Cardiology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands
19. Department of Cardiology, University Medical Center, Belgrade, Serbia
20. Department of Cardiology, Freeman Hospital, Newcastle upon Tyne, UK
21. Cardiac Imaging Unit, Ramón y Cajal University Hospital, Madrid, Spain
22. Division of Cardiology, Department of Cardiological Thoracic and Vascular Sciences, University of Padova, Padova, Italy.
23. Université de Versailles-Saint Quentin, Hôpital Ambroise Paré, AP-HP, Boulogne-Billancourt, France
24. AP-HP, Hôpital Pitié-Salpêtrière, Paris, France