ESC Guidelines on Hypertrophic Cardiomyopathy

Authors/Task Force members: Perry M. Elliott (Chairperson) (UK), Aris Anastasakis (Greece), Michael A. Borger (Germany), Martin Borggrefe (Germany), Franco Cecchi (Italy), Philippe Charron (France), Albert Alain Hagege (France), Antoine Lafont (France), Giuseppe Limongelli (Italy), Heiko Mahrholdt (Germany), William J. McKenna (UK), Jens Mogensen (Denmark), Petros Nihoyannopoulos (UK), Stefano Nistri (Italy), Petronella G. Pieper (Netherlands), Burkert Pieske (Austria), Claudio Rapezzi (Italy), Frans H. Rutten (Netherlands), Christoph Tillmanns (Germany), and Hugh Watkins (UK).
Additional Contributor: Constantinos O'Mahony (UK).
Cardiomyopathy: Definition

- “A myocardial disorder in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease, hypertension, valvular disease and congenital heart disease sufficient to cause the observed myocardial abnormality.”
**HCM: Diagnostic criteria**

*Increased left ventricular wall thickness not solely explained by abnormal loading conditions*

**ADULTS:**
- LV wall thickness ≥15 mm in one or more LV myocardial segments measured by any imaging technique (echocardiography, cardiac magnetic resonance imaging (CMR) or computed tomography (CT) that is not explained solely by loading conditions.

**CHILDREN:**
- LV wall thickness more than two standard deviations above the predicted mean (z-score >2, where a z-score is defined as the number of standard deviations from the population mean)

**RELATIVES (adults):**
- Unexplained increased LV wall thickness ≥13 mm in one or more LV myocardial segments measured by any imaging technique
## Management of HCM

<table>
<thead>
<tr>
<th>Initial assessment</th>
<th>Therapeutics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive / differential diagnosis</td>
<td>Sport activity, life style</td>
</tr>
<tr>
<td>Diagnosis of aetiology</td>
<td>TTT of symptoms</td>
</tr>
<tr>
<td>Investigation of symptoms</td>
<td>SCD prevention</td>
</tr>
<tr>
<td>Risk stratification</td>
<td>TTT of complications</td>
</tr>
<tr>
<td>Genetic counselling and testing</td>
<td>Reproduction, maternal risk</td>
</tr>
</tbody>
</table>
AETIOLOGY
HCM: Aetiological heterogeneity

Genetic and sarcomeric etiology

Genetic mutations in sarcomeric protein genes account for the majority of cases in adolescents and adults. Genetic causes are listed below:

- Inborn errors of metabolism
  - Glycogen storage diseases
    - Pompe
    - Danon
  - AMP-kinase (PRKAG2)
  - Carnitine disorders
  - Lysosomal storage diseases
    - Anderson-Fabry
  - Neuromuscular diseases
    - Friedreich’s ataxia
    - TH1
  - Mitochondrial diseases
    - MELAS
    - MERFF
  - Malformation Syndromes
    - Noonan
    - LEOPARD
    - Costello
    - CFC
  - Amyloidosis
    - Familial ATTR
    - Wild type TTR (senile)
    - AL amyloidosis
  - Newborn of diabetic mother
  - Drug-induced
    - Tacrolimus
    - Hydroxychloroquine
    - Steroids

Sarcomeric protein gene mutation: 40–60%

Unknown: ~ 25–30%

~ 5–10%

Other genetic and non-genetic causes

- MYL3
- TPM1
- TNNI3
- TNNT2
- MYH7
- MYBPC3

(Troponin T)

(Beta myosin heavy chain)

(Myosin binding protein C)
General approach to the diagnosis of hypertrophic cardiomyopathy

- **Clinical evaluation**
  - Pedigree
  - Signs
  - Symptoms
  - ECG
  - Cardiac Imaging
  - Laboratory

- **Diagnostic red flags**
  - Features suggesting a specific disease?

- **Genetic testing**
  - Consider genetic testing
    - Definite disease causing sarcomere protein gene mutation
    - No definite disease causing sarcomere protein identified

- **Further specialised tests & multidisciplinary input**
  - Specific genetic/acquired disorder

- **No cause identified**
  - Reconsider other genetic/non genetic causes
# History and Physical Examination

<table>
<thead>
<tr>
<th>Symptom/sign</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gait disturbance</td>
<td>• Friedreich’s ataxia</td>
</tr>
</tbody>
</table>
| Paraesthesia/sensory abnormalities/neuropathic pain | • Amyloidosis  
• Anderson-Fabry disease |
| **Carpal tunnel syndrome** | • TTR-related amyloidosis (especially when bilateral and in male patients) |
| Muscle weakness | • Mitochondrial diseases  
• Glycogen storage disorders  
• FH1I mutations  
• Friedreich’s ataxia |
| Palpebral ptosis | • Mitochondrial diseases  
• Noonan/LEOPARD syndrome  
• Myotonic dystrophy |
| Lentigines/café au lait spots | • LEOPARD/Noonan syndrome |
| Angiokeratomata, hypohidrosis | • Anderson-Fabry disease |

- **How old is the patient?**
- **Family history?**
- **Non-cardiac symptoms & signs?**
# Electrocardiographic abnormalities suggesting specific diagnoses

<table>
<thead>
<tr>
<th>Finding</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short PR interval/pre-excitation</td>
<td>Pre-excitation is a common feature of storage diseases (Pompe, PRKAG2, and Danon) and mitochondrial disorders (MELAS, MERFF). A short PR interval without pre-excitation is seen in Anderson-Fabry disease.</td>
</tr>
<tr>
<td>AV block</td>
<td>Progressive atrioventricular conduction delay is common in mitochondrial disorders, some storage diseases (including Anderson-Fabry disease), amyloidosis, desminopathies and in patients with PRKAG2 mutations.</td>
</tr>
<tr>
<td>Extreme LVH (Sokolow score ≥50)</td>
<td>Extremely large QRS voltage is typical of storage diseases such as Pompe and Danon disease, but can be caused by pre-excitation alone.</td>
</tr>
<tr>
<td>Low QRS voltage (or normal voltages despite increased LV wall thickness)</td>
<td>Low QRS voltage in the absence of pericardial effusion, obesity and lung disease is rare in HCM (limited to cases with end-stage evolution) but is found in up to 50% of patients with AL amyloidosis and 20% with TTR amyloidosis. Differential diagnosis between HCM and cardiac amyloidosis is aided by measuring the ratio between QRS voltages and LV wall thickness.</td>
</tr>
</tbody>
</table>
Echocardiography: Differential Diagnosis

<table>
<thead>
<tr>
<th>Finding</th>
<th>Specific diseases to be considered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased interatrial septum thickness</td>
<td>Amyloidosis</td>
</tr>
<tr>
<td>Increased AV valve thickness</td>
<td>Amyloidosis; Anderson-Fabry disease</td>
</tr>
<tr>
<td>Increased RV free wall thickness</td>
<td>Amyloidosis, myocarditis, Anderson-Fabry disease, Noonan syndrome and related disorders</td>
</tr>
<tr>
<td>Mild to moderate pericardial effusion</td>
<td>Amyloidosis, myocarditis</td>
</tr>
<tr>
<td>Ground-glass appearance of ventricular myocardium on 2-D echocardiography</td>
<td>Amyloidosis</td>
</tr>
<tr>
<td>Concentric LVH</td>
<td>Glycogen storage disease, Anderson-Fabry disease, PRKAG2 mutations</td>
</tr>
<tr>
<td>Extreme concentric LVH (wall thickness ≥ 30 mm)</td>
<td>Danon disease, Pompe disease</td>
</tr>
<tr>
<td>Global LV hypokinesia (with or without LV dilatation)</td>
<td>Mitochondrial disease, TTR-related amyloidosis, PRKAG2 mutations, Danon disease, myocarditis, advanced sarcomeric HCM, Anderson-Fabry disease</td>
</tr>
<tr>
<td>Right ventricular outflow tract obstruction</td>
<td>Noonan syndrome and associated disorders</td>
</tr>
</tbody>
</table>

Interpret images in context of clinical features and other tests.
Cardiac Magnetic Resonance Imaging

CMR should be considered in patients with HCM at their baseline assessment if local resources and expertise permit.

Morphological evaluation:
- LV morphology and function

Etiological diagnosis:

Prognostic value:
- The extend of LGE has some utility in predicting cardiovascular mortality but current data do not support the use of LGE in sudden cardiac death prediction

CMR with LGE imaging should be considered in patients with suspected cardiac amyloidosis.

IIa  C

www.escardio.org/guidelines

ASSESSMENT OF SYMPTOMS
Assessment of LVOTO should be part of the routine evaluation of all symptomatic patients.
MANAGEMENT OF SYMPTOMS

**Beta BLOCKERS**, as first line

If contra indication or second line: **verapamil** (Isoptine)
Echocardiography: LV Outflow Tract Obstruction

✓ About 30% of patients have gradient at rest
✓ About 30% of patients have latent obstruction (provoked by manoeuvres that reduce preload or afterload: standing from squat, Valsalva, exercise)
✓ Clinically significant if $\geq 50$ mmHg

2-D and Doppler echocardiography at rest, Valsalva and standing

- Maximum provoked peak LVOTO $\geq 50$ mmHg
  - (see 9.1 Symptomatic left ventricular outflow tract obstruction)
  - Asymptomatic
    - Repeat echocardiography 1 year
- Maximum provoked peak LVOTO $< 50$ mmHg
  - Symptomatic
    - Exercise stress echocardiography
  - Medical therapy
    (see Chap 9. Management of Symptoms and complications)

*exercise echocardiography may be considered in individual patients when the presence of a LVOT gradient is relevant to lifestyle advice and decisions on medical treatment. LVOTO = left ventricular outflow tract obstruction.

www.escardio.org/guidelines

Management of persistent symptoms (1)

LEFT VENTRICULAR OUTFLOW TRACT OBSTRUCTION
Treatment of Left Ventricular Outflow Tract Obstruction

- By convention, LVOTO is defined as a peak instantaneous Doppler LV outflow tract gradient of ≥30 mm Hg, but the threshold for invasive treatment is usually considered to be ≥50 mm Hg.

- There are no data to support the use of invasive procedures to reduce LV outflow obstruction in asymptomatic patients, regardless of its severity.

- Arterial and veinous vasodilatorators should be avoided, digoxin is not recommended
Treatment of LV Outflow Tract Obstruction

<table>
<thead>
<tr>
<th>Disopyramide, titrated to maximum tolerated dose, if persistent symptoms and LVOT</th>
<th>I</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disopyramide</strong>, titrated to maximum tolerated dose, if persistent symptoms and LVOT</td>
<td>Iib</td>
<td>C</td>
</tr>
</tbody>
</table>

Disopyramide (Rythmodan):
if persistent symptoms and LVOT

Low-dose loop- or thiazide diuretics may be used with caution in symptomatic LVOTO, to improve exertional dyspnoea.

www.escardio.org/guidelines

Invasive Treatment of LV Outflow Tract Obstruction

Experienced multidisciplinary teams should assess all patients before Intervention

Surgeons and cardiologists who perform invasive gradient reduction therapies should be trained in experienced centres and work as part of a multidisciplinary team experienced in the management of HCM.

Figure 5 Pre-assessment checklist for patients being considered for invasive septal reduction therapies

- Obesity
- Respiratory disease
- Coronary artery disease
- Anaemia
- Thyroid disease
- Arrhythmia (e.g. AF)
- Drug side-effects
- Systemic disease (e.g. amyloid)
- RVOT obstruction

- SAM-related
- Mid-cavity
- Sub-aortic membrane
- Aortic stenosis
- Anomalous papillary muscle insertion
- Accessory mitral valve tissue

- Mitral prolapse
- Other intrinsic MV abnormality

Assess mitral valve anatomy/function

Assess distribution and severity of hypertrophy

Minimum anterior septal thickness >17mm

AF = atrial fibrillation; MV = mitral valve; RVOT = right ventricular outflow tract; SAM = systolic anterior motion of the mitral valve.
## Invasive Treatment of LV Outflow Tract Obstruction

### Recommendations on septal reduction therapy

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>It is recommended that septal reduction therapies be performed by experienced operators working as part of a multidisciplinary team expert in the management of HCM.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Septal reduction therapy to improve symptoms is recommended in patients with a resting or maximum provoked LVOT gradient of ≥50 mmHg, who are in NYHA functional Class III-IV despite maximum tolerated medical therapy.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Septal reduction therapy should be considered in patients with recurrent exertional syncope caused by a resting or maximum provoked LVOTO gradient ≥50 mmHg despite optimal medical therapy.</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Septal myectomy, rather than SAA, is recommended in patients with an indication for septal reduction therapy and other lesions requiring surgical intervention (e.g., mitral valve repair/replacement, papillary muscle intervention).</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Mitral valve repair or replacement should be considered in symptomatic patients with a resting or maximum provoked LVOTO gradient ≥50 mmHg and moderate-to-severe mitral regurgitation not caused by SAM of the mitral valve alone.</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Mitral valve repair or replacement may be considered in patients with a resting or maximum provoked LVOTO gradient ≥50 mmHg and a maximum septal thickness ≤16 mm at the point of the mitral leaflet-septal contact or when there is moderate-to-severe mitral regurgitation following isolated myectomy.</td>
<td>IIb</td>
<td>C</td>
</tr>
</tbody>
</table>
### Recommendations on indications for cardiac pacing in patients with obstruction

<table>
<thead>
<tr>
<th>Class&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Level&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIb</td>
<td>C</td>
</tr>
</tbody>
</table>

**Sequential AV pacing**, with optimal AV interval to reduce the LV outflow tract gradient or to facilitate medical treatment with β-blockers and/or verapamil, may be considered in selected patients with resting or provokable LVOTO $\geq 50$ mmHg, sinus rhythm and drug-refractory symptoms, who have contra-indications for septal alcohol ablation or septal myectomy or are at high-risk of developing heart block following septal alcohol ablation or septal myectomy.

In patients with resting or provokable LVOTO $\geq 50$ mmHg, sinus rhythm and drug-refractory symptoms, in whom there is an indication for an ICD, a dual-chamber ICD (instead of a single-lead device) may be considered, to reduce the LV outflow tract gradient or to facilitate medical treatment with β-blockers and/or verapamil.
Management of persistent symptoms (2)

NON-OBSTRUCTIVE HCM
Management of Heart Failure Symptoms in Non-Obstructive HCM

Figure 6 Algorithm for the treatment of heart failure in hypertrophic cardiomyopathy.

Heart Failure
NYHA Class II–IV

Resting or provokable LVOTO ≥50 mmHg

Management of LVOTO

Resting or provokable LVOTO <50 mmHg

AF?

Rate/Rhythm control anticoagulation

LVEF ≥50%

β-blockers, verapamil or diltiazem
Low-dose loop and thiazide diuretics

Consider cardiac transplantation

LVEF <50%

β-blockers, ACEi, MRA
Low-dose loop and thiazide diuretics

ACEi = angiotensin converting enzyme inhibitor; AF = atrial fibrillation; LVEF = left ventricular ejection fraction;
LVOTO = left ventricular outflow tract obstruction; MRA = mineralocorticoid receptor antagonist;
NYHA = New York Heart Association functional class.
SUDDEN CARDIAC DEATH
Sudden Cardiac Death in HCM

- Annual incidence for cardiovascular death of 1–2%, with sudden cardiac death (SCD), heart failure and thromboembolism being the main causes of death.

- In adolescents and adults, the risk assessment should comprise of:
  - clinical and family history,
  - 48-hour ambulatory ECG,
  - TTE (or CMR in the case of poor echo windows)
  - and a symptom-limited exercise test.
Risk Factors for Sudden Cardiac Death (Adults)

- Non-sustained Ventricular Tachycardia
- Severity of LV wall thickness (>30 mm)
- Family History of Sudden Cardiac Death (age < 40y)
- Unexplained syncope (non vasovagal)
- Exercise Blood Pressure Response (delta PAS < 20-25 mmHg)
- Young Age
- Left Atrial Diameter
- Left Ventricular Outflow Tract Obstruction
- Some mutations etc…
Prevention of SCD in Hypertrophic Cardiomyopathy

- There are no randomized trials or statistically validated prospective prediction models that can be used to guide ICD implantation in patients with HCM.


HCM Risk-SCD model for predicting 5 year risk

\[
\text{Probability} \ SCD \ at \ 5 \ years = 1 - 0.998^{\exp(\text{prognostic index})}
\]

where Prognostic index = [0.15939858 x maximal wall thickness (mm)] – [0.00294271 x maximal wall thickness² (mm²)] + [0.0259082 x left atrial diameter (mm)] + [0.00446131 x maximal (rest/Valsalva) left ventricular outflow tract gradient (mmHg)] + [0.4583082 x family history SCD] + [0.82639195 x NSVT] + [0.71650361 x unexplained syncope] – [0.01799934 x age at clinical evaluation (years)].
HCM Risk-SCD: Predictor variables


<table>
<thead>
<tr>
<th>Predictor Variable</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at evaluation.</td>
<td></td>
</tr>
<tr>
<td>History of sudden cardiac death in one or more first degree relatives under 40 years of age or SCD in a first degree relative with confirmed HCM at any age (post or ante-mortem diagnosis).</td>
<td></td>
</tr>
<tr>
<td><strong>Maximal wall thickness</strong>: the greatest thickness in the anterior septum, posterior septum, lateral wall, and posterior wall of the LV, measured at the level of the mitral valve, papillary muscles and apex using parasternal short-axis plane using 2-D echocardiography.</td>
<td></td>
</tr>
<tr>
<td>Left atrial diameter determined by M-Mode or 2D echocardiography in the parasternal long axis plane.</td>
<td></td>
</tr>
<tr>
<td>The maximum LV outflow gradient determined at rest and with Valsalva provocation (irrespective of concurrent medical treatment) using pulsed and continuous wave Doppler from the apical three and five chamber views. Peak outflow tract gradients were determined using the modified Bernoulli equation: Gradient= 4V², where V is the peak aortic outflow velocity.</td>
<td></td>
</tr>
<tr>
<td>NSVT: ≥3 consecutive ventricular beats at a rate of ≥120 beats per minute and &lt;30s in duration on Holter monitoring (minimum duration 24 hours) at or prior to evaluation.</td>
<td></td>
</tr>
<tr>
<td>History of unexplained syncope at or prior to evaluation.</td>
<td></td>
</tr>
</tbody>
</table>

On line calculator: [Absolute risk of SCD at 5 years](www.escardio.org/guidelines)

Prevention of Sudden Cardiac Death

Recommendations for ICD in each risk category take into account not only the absolute statistical risk, but also the age and general health of the patient, socio-economic factors and the psychological impact of therapy.
GENETIC COUNSELLING & TESTING
Genetic Counselling

Help the individual or the family to understand the options for dealing with the risk of recurrence and choose the action which is appropriate to them.  

Godard et al. Eur J Hum Genet 2003

- Understand medical, psychological, social, professional, ethical & legal implications of a genetic diagnosis.  

Charron et al. ESC WG Statement. Eur Heart J 2010;31(22):2715

**Recommendations on genetic counselling**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Class a</th>
<th>Level b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic counselling is recommended for all patients with HCM when their disease cannot be explained solely by a non-genetic cause, whether or not clinical or genetic testing will be used to screen family members.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Genetic counselling should be performed by professionals trained for this specific task working within a multidisciplinary specialist team.</td>
<td>IIa</td>
<td>C</td>
</tr>
</tbody>
</table>
**Web Table 2:** Main genes associated with familial hypertrophic cardiomyopathy (Online Mendelian Inheritance in Man OMIM phenotypic series, 192600)\(^{21}\)

<table>
<thead>
<tr>
<th>Protein</th>
<th>Gene</th>
<th>Location</th>
<th>MIM gene</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myosin-7 (β-myosin heavy chain)</td>
<td>MYH7</td>
<td>14q11.2</td>
<td>160760</td>
<td>10–20%</td>
</tr>
<tr>
<td>Myosin-binding protein C, cardiac-type</td>
<td>MYBPC3</td>
<td>11p11.2</td>
<td>600958</td>
<td>15–30%</td>
</tr>
<tr>
<td>Troponin T, cardiac muscle</td>
<td>TNNT2</td>
<td>1q32.1</td>
<td>191045</td>
<td>3–5%</td>
</tr>
<tr>
<td>Troponin I, cardiac muscle</td>
<td>TNNI3</td>
<td>19q13.42</td>
<td>191044</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Troponymosin alpha-1 chain</td>
<td>TPM1</td>
<td>15q22.2</td>
<td>191010</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Myosin regulatory light chain 2, ventricular/cardiac muscle isoform</td>
<td>MYL2</td>
<td>12q24.11</td>
<td>160781</td>
<td></td>
</tr>
<tr>
<td>Myosin light chain 3</td>
<td>MYL3</td>
<td>3p21.31</td>
<td>160790</td>
<td>1%</td>
</tr>
<tr>
<td>Actin, alpha cardiac muscle 1</td>
<td>ACTC1</td>
<td>15q14</td>
<td>102540</td>
<td></td>
</tr>
<tr>
<td>Cysteine and glycine-rich protein 3, muscle LIM protein</td>
<td>CSRPL3</td>
<td>1p15.1</td>
<td>600824</td>
<td></td>
</tr>
<tr>
<td>Titin</td>
<td>TTN</td>
<td>2q31.2</td>
<td>188840</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Cardiac phospholamban</td>
<td>PLN</td>
<td>6q22.31</td>
<td>172405</td>
<td></td>
</tr>
<tr>
<td>5’-AMP-activated protein kinase subunit gamma-2</td>
<td>PRKAG2</td>
<td>7q36.1</td>
<td>602743</td>
<td>1%</td>
</tr>
<tr>
<td>Alpha galactosidase A (Anderson, Fabry disease)</td>
<td>GLA</td>
<td>Xq22.1</td>
<td>300644</td>
<td>1–3%</td>
</tr>
<tr>
<td>Lysosome membrane associated protein 2 (Danco disease)</td>
<td>LAMP2</td>
<td>Xq24</td>
<td>309060</td>
<td>0.7%–2.7%</td>
</tr>
</tbody>
</table>

[www.escardio.org/guidelines](http://www.escardio.org/guidelines)  
Genetic Testing

- Genetic testing is recommended in patients fulfilling diagnostic criteria for HCM to enable cascade genetic screening of their relatives.

- When a definite causative genetic mutation is identified in a patient, his or her relatives should first be genetically tested, and then clinically evaluated if they are found to carry the same mutation.
Flow chart for genetic and clinical screening of probands and relatives.

- Genetic testing
  - Definite mutation
    - Cascade genetic test
      - Mutation positive ± clinical phenotype
        - Long-term follow-up
      - Mutation negative
        - Discharge
  - Variant of unknown/uncertain significance
    - Segregation analysis where possible
  - No mutation
    - Reconsider other genocopies/phenocopies
      - Cascade clinical screening
        - HCM
          - Long-term follow-up
        - Normal
          - Repeat screening at intervals

HCM = hypertrophic cardiomyopathy.
Cascade genetic test = screening of first degree relatives of patients already diagnosed with HCM.
Other potential indications for genetic testing in probands

- Accurate diagnosis of HCM subtype (non sarcomeric)
- Accurate diagnosis in ambiguous situations (e.g. borderline phenotype, SCD and preclinical stage)
- Manage procreative issues (prenatal diagnosis, pre-implantation diagnosis)
- Prognostic evaluation (some phenotype-genotype correlations, sarcomeric versus non sarcomeric HCM, multiple mutations)
ESC Guidelines on HCM

Authors/Task Force members: Perry M. Elliott (Chairperson) (UK), Aris Anastasakis (Greece), Michael A. Borger (Germany), Martin Borggreve (Germany), Franco Cecchi (Italy), Philippe Charron (France), Albert Alain Hagege (France), Antoine Lafont (France), Giuseppe Limongelli (Italy), Heiko Mahrholdt (Germany), William J. McKenna (UK), Jens Mogensen (Denmark), Petros Nihoyannopoulos (UK), Stefano Nistri (Italy), Petronella G. Pieper (Netherlands), Burkert Pieske (Austria), Claudio Rapezzi (Italy), Frans H. Rutten (Netherlands), Christoph Tillmanns (Germany), and Hugh Watkins (UK).
Additional Contributor: Constantinos O'Mahony (UK).

Pr Philippe Charron
philippe.charron@psl.aphp.fr

www.escardio.org/guidelines

### Classes of recommendations

<table>
<thead>
<tr>
<th>Classes of recommendations</th>
<th>Definition</th>
<th>Suggested wording to use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Classe I</strong></td>
<td>Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.</td>
<td>Is recommended/is indicated.</td>
</tr>
<tr>
<td><strong>Class II</strong></td>
<td>Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.</td>
<td></td>
</tr>
<tr>
<td><strong>Class IIa</strong></td>
<td><strong>Weight of evidence/opinion is in favour of usefulness/efficacy.</strong></td>
<td>Should be considered.</td>
</tr>
<tr>
<td><strong>Class IIb</strong></td>
<td><strong>Usefulness/efficacy is less well established by evidence/opinion.</strong></td>
<td>May be considered.</td>
</tr>
<tr>
<td><strong>Class III</strong></td>
<td>Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.</td>
<td>Is not recommended.</td>
</tr>
</tbody>
</table>
# Levels of evidence

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of Evidence A</td>
<td>Data derived from multiple randomized clinical trials or meta-analyses.</td>
</tr>
<tr>
<td>Level of Evidence B</td>
<td>Data derived from a single randomized clinical trial or large non-randomized studies.</td>
</tr>
<tr>
<td>Level of Evidence C</td>
<td>Consensus of opinion of the experts and/or small studies, retrospective studies, registries.</td>
</tr>
</tbody>
</table>
Acknowledgements

ESC Committee for Practice Guidelines (CPG): Jose Luis Zamorano (Chairperson) (Spain), Stephan Achenbach (Germany), Helmut Baumgartner (Germany), Jeroen Bax (Netherlands), Héctor Bueno (Spain), Veronica Dean (France), Christi Deaton (UK), Çetin Erol (Turkey), Robert Fagard (Belgium), Roberto Ferrari (Italy), David Hasdai (Israel), Arno W. Hoes (Netherlands), Paulus Kirchhof (Germany/UK), Juhani Knuuti (Finland), Philippe Kolh (Belgium), Patrizio Lancellotti (Belgium), Ales Linhart (Czech Republic), Petros Nihoyannopoulos (UK), Massimo F. Piepoli (Italy), Piotr Ponikowski (Poland), Per Anton Sirnes (Norway), Juan Luis Tamargo (Spain), Michal Tendera (Poland), Adam Torbicki (Poland), William Wijns (Belgium), and Stephan Windecker (Switzerland).

Document Reviewers: David Hasdai (Israel) (CPG Review Coordinator), Piotr Ponikowski (Poland) (CPG Review Coordinator), Stephan Achenbach (Germany), Fernando Alfonso (Spain), Cristina Basso (Italy), Nuno Miguel Cardim (Portugal), Juan Ramón Gimeno (Spain), Stephane Heymans (Netherlands), Per Johan Holm (Sweden), Andre Keren (Israel), Paulus Kirchhof (Germany/UK), Philippe Kolh (Belgium), Christos Lionis (Crete), Claudio Muneretto (Italy), Silvia Priori (Italy), Maria Jesus Salvador (Spain), Christian Wolpert (Germany), and Jose Luis Zamorano (Spain).

National Cardiac Societies document reviewers