Βραχέα μηνύματα για την πρόληψη αιφνιδιου καρδιακού θανάτου
Σε ασθενή με υπερτροφική μυοκαρδιοπάθεια

Ι.Σκιαδάς
Ιπποκράτειο Αθηνών
Δήλωση συμφερόντων: • Καμία prevalence of unexplained increase in LV thickness in the range of 0.02–0.23% in adults
Pathophysiology of HCM

- ↑myofilament activation / myocyte contractility (↑Ca\text{2+} sensitivity; ↑sliding speed of filaments; ↑force generated) and ↑use of energy (ATP consumption)
- Compromised energetics of cardiomyocyte: ↑sarcoplasmic Ca\text{2+} during diastole, abnormal excitation-contraction coupling; early diastolic dysfunction
- Stimulation of signaling pathways (calcineurin-NFAT) that promote hypertrophy
- Abnormal tissue architecture and gross hypertrophy

Watkins et al. NEJM 2011;364: 1643-56
Diverse aetiology of hypertrophic cardiomyopathy

- MYL3
- TPM1
- TNN13
- TNNT3
- MYH7
- MYBPC3

Sarcomeric protein gene mutation 40-60%

Unknown ~ 25-30%

Other genetic and non-genetic causes:

- Inborn errors of metabolism
  - Glycogen storage diseases:
    - Pompe
    - Danon
  - AMP-Kinase (PRKAG2)
  - Carnitine disorders
  - Lysosomal storage diseases:
    - Anderson-Fabry
    - FHL1
  - Neuromuscular diseases
    - Friedreich’s ataxia
  - Mitochondrial diseases:
    - MELAS
    - MERRF
  - Malformation Syndromes
    - Noonan
    - LEOPARD
    - Costello
    - CFC
  - Amyloidosis
    - Familial ATTR
    - Wild type TTR (senile)
    - AL amyloidosis
  - Newborn of diabetic mother
  - Drug-induced
    - Tacrolimus
    - Hydroxychloroquine
    - Steroids

The majority of cases in adolescents and adults are caused by mutations in sarcomere protein genes.
Figure 2. Prognosis profiles for HCM and targets for therapy. AF indicates atrial fibrillation. Modified with permission from Maron et al.\textsuperscript{10}
ΔΕΥΤΕΡΟΓΕΝΗΣ ΠΡΟΛΗΨΗ
10.6% annual intervention rate

39% 5-year cumulative probability
### Table 2. Risk Factors for Sudden Death in HCM*

<table>
<thead>
<tr>
<th>Major</th>
<th>Possible in Individual Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac arrest (ventricular fibrillation)</td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>Spontaneous sustained ventricular tachycardia</td>
<td>Myocardial ischemia</td>
</tr>
<tr>
<td>Family history of premature sudden death</td>
<td>LV outflow obstruction</td>
</tr>
<tr>
<td>Unexplained syncope</td>
<td>High-risk mutation</td>
</tr>
<tr>
<td>LV thickness greater than or equal to 30 mm</td>
<td>Intense (competitive) physical exertion</td>
</tr>
<tr>
<td>Abnormal exercise blood pressure</td>
<td></td>
</tr>
<tr>
<td>Nonsustained ventricular tachycardia (Holter)</td>
<td></td>
</tr>
</tbody>
</table>

*See text for details.

HCM = hypertrophic cardiomyopathy; LV = left ventricular.

**ICD: 2 or more risk factors**
2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy

Other SCD Risk Modifiers

1. LVOT obstruction
2. LGE and CMR
3. LV apical aneurysm
4. Genetic mutations
Outcome and Complications After Implantable Cardioverter Defibrillator Therapy in Hypertrophic Cardiomyopathy
Systematic Review and Meta-Analysis

Arend F.L. Schinkel, MD, PhD; Pieter A. Vriesendorp, MD; Eric J.G. Sijbrands, MD, PhD; Luc J.L.M. Jordaens, MD, PhD; Folkert J. ten Cate, MD, PhD; Michelle Michels, MD, PhD

(Circ Heart Fail. 2012;5:552-559.)
A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM Risk-SCD)

Constantinos O’Mahony¹, Fatima Jichi², Menelaos Pavlou³, Lorenzo Monserrat³, Aristides Anastasakis⁴, Claudio Ravezzi⁵, Elena Biagini⁵, Juan Ramon Gimeno⁶, Giuseppe Limongelli⁷, William J. McKenna¹, Rumana Z. Omar²,⁸ and Perry M. Elliott¹*

Table 2: Cohort characteristics

<table>
<thead>
<tr>
<th>Baseline</th>
<th>All</th>
<th>The Heart Hospital, UK</th>
<th>A Coruña University Hospital, Spain</th>
<th>1St Department of Cardiology, University of Athens, Greece</th>
<th>Institute of Cardiology, Bologna, Italy</th>
<th>University Hospital Virgen de la Arrixaca, Spain</th>
<th>Monaldi Hospital, Italy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>3675</td>
<td>1593 (43%)</td>
<td>590 (16%)</td>
<td>474 (13%)</td>
<td>456 (12%)</td>
<td>406 (11%)</td>
<td>156 (4%)</td>
</tr>
<tr>
<td>Male</td>
<td>2349 (64%)</td>
<td>1,018 (64%)</td>
<td>364 (62%)</td>
<td>340 (72%)</td>
<td>292 (64%)</td>
<td>243 (60%)</td>
<td>92 (59%)</td>
</tr>
<tr>
<td>Age; years¹</td>
<td>48 ± 17</td>
<td>43 ± 15</td>
<td>57 ± 15</td>
<td>47 ± 16</td>
<td>50 ± 17</td>
<td>82 (20%)</td>
<td>44 ± 16</td>
</tr>
<tr>
<td>NYHA III/IV</td>
<td>426 (12%)</td>
<td>427 (8.5%)</td>
<td>76 (13%)</td>
<td>77 (16%)</td>
<td>41 (9%)</td>
<td>39 (10%)</td>
<td>14 (9%)</td>
</tr>
<tr>
<td>Myectomy</td>
<td>34 (1%)</td>
<td>17 (1%)</td>
<td>6 (1%)</td>
<td>1 (0.2%)</td>
<td>5 (1%)</td>
<td>2 (0.5%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Alcohol septal ablation</td>
<td>10 (0.3%)</td>
<td>4 (0.3%)</td>
<td>2 (0.3%)</td>
<td>0</td>
<td>2 (0.4%)</td>
<td>2 (0.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>468 (13%)</td>
<td>217 (14%)</td>
<td>79 (13%)</td>
<td>44 (9%)</td>
<td>78 (17%)</td>
<td>39 (10%)</td>
<td>11 (7%)</td>
</tr>
<tr>
<td>ICD</td>
<td>42 (1%)</td>
<td>14 (1%)</td>
<td>6 (1%)</td>
<td>1 (0.2%)</td>
<td>5 (1%)</td>
<td>8 (2%)</td>
<td>8 (5%)</td>
</tr>
<tr>
<td>Permanent/persistent AF</td>
<td>366 (10%)</td>
<td>98 (6%)</td>
<td>133 (23%)</td>
<td>39 (8%)</td>
<td>19 (4%)</td>
<td>65 (16%)</td>
<td>12 (8%)</td>
</tr>
<tr>
<td>NSVT</td>
<td>634 (17%)</td>
<td>300 (19%)</td>
<td>82 (14%)</td>
<td>56 (12%)</td>
<td>80 (18%)</td>
<td>85 (21%)</td>
<td>31 (20%)</td>
</tr>
<tr>
<td>LA diameter; mm²</td>
<td>44 ± 8</td>
<td>44 ± 8</td>
<td>45 ± 8</td>
<td>44 ± 6</td>
<td>46 ± 9</td>
<td>44 ± 8</td>
<td>45 ± 8</td>
</tr>
<tr>
<td>LVOTGmax; mmHg²</td>
<td>12 ± 5 (46)</td>
<td>9 ± 5 (46)</td>
<td>10 ± 7 (46)</td>
<td>10 ± 4 (60)</td>
<td>20 (15–50)</td>
<td>4 (4–60)</td>
<td>4 (4–40)</td>
</tr>
<tr>
<td>LVeddd; mm</td>
<td>45 ± 7</td>
<td>44 ± 6</td>
<td>45 ± 6</td>
<td>47 ± 5</td>
<td>44 ± 7</td>
<td>44 ± 7</td>
<td>46 ± 5</td>
</tr>
<tr>
<td>MWT; mm²</td>
<td>20 ± 5</td>
<td>20 ± 6</td>
<td>20 ± 6</td>
<td>18 ± 4</td>
<td>20 ± 5</td>
<td>20 ± 5</td>
<td>20 ± 5</td>
</tr>
<tr>
<td>FS; %</td>
<td>41 ± 9</td>
<td>42 ± 9</td>
<td>41 ± 9</td>
<td>41 ± 7</td>
<td>41 ± 11</td>
<td>39 ± 10</td>
<td>32 ± 11</td>
</tr>
<tr>
<td>FHSCD</td>
<td>886 (24%)</td>
<td>482 (30%)</td>
<td>42 (7%)</td>
<td>147 (31%)</td>
<td>69 (15%)</td>
<td>110 (27%)</td>
<td>36 (23%)</td>
</tr>
<tr>
<td>Unexplained syncope</td>
<td>507 (14%)</td>
<td>274 (17%)</td>
<td>55 (9%)</td>
<td>90 (19%)</td>
<td>11 (2%)</td>
<td>55 (14%)</td>
<td>22 (14%)</td>
</tr>
</tbody>
</table>
5-year risk of SCD using the HCM Risk-SCD model

**Probability** \(P_{SCD \text{ at } 5 \text{ years}} = 1 - 0.998 \exp(\text{Prognostic index})\)

where Prognostic index = \(0.15939858 \times \text{maximal wall thickness (mm)}\)
- \(0.00294271 \times \text{maximal wall thickness}^2 \text{ (mm}^2)\) + \(0.0259082 \times \text{left atrial diameter (mm)}\)
+ \(0.00446131 \times \text{maximal (rest/Valsalva) left ventricular outflow tract gradient (mm Hg)}\)
+ \(0.4583082 \times \text{family history SCD}\)
+ \(0.82639195 \times \text{NSVT}\) + \(0.71650361 \times \text{unexplained syncope}\)
- \(0.01799934 \times \text{age at clinical evaluation (years)}\)
Flow chart for ICD implantation

**PRIMARY PREVENTION**

Recommended assessment:
- History
- 2-D/Doppler echocardiogram
- 48-hour ambulatory ECG

HCM Risk-SCD variables:
- Age
- Family history of sudden cardiac death
- Unexplained syncope
- Left ventricular outflow gradient\(^a\)
- Maximum left ventricular wall thickness\(^a\)
- Left atrial diameter\(^a\)
- NSVT

HCM Risk-SCD Score

**SECONDARY PREVENTION**

- Cardiac arrest due to VT or VF
- Spontaneous sustained VT causing syncope or haemodynamic compromise

Life expectancy >1 year

ICD recommended

\(^a\) Use absolute values for LVOT gradient, MLVWT and left atrial dimension.

www.escardio.org/guidelines

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>• The effect of age on SCD has been examined in a number of studies, and two have shown a significant association, with an increased risk of SCD in younger patients. Some risk factors appear to be more important in younger patients, most notably, NSVT, severe LVH, and unexplained syncpe.</td>
</tr>
<tr>
<td><strong>Non-sustained ventricular tachycardia</strong></td>
<td>• NSVT (defined as ≥3 consecutive ventricular beats at ≥120 BPM lasting &lt;30 seconds) occurs in 20–30% of patients during ambulatory ECG monitoring and is an independent predictor of SCD. There is no evidence that the frequency, duration or rate of NSVT influences the risk of SCD.</td>
</tr>
<tr>
<td><strong>Maximum left ventricular wall thickness</strong></td>
<td>• The severity and extent of LVH measured by TTE are associated with the risk of SCD. Several studies have shown the greatest risk of SCD in patients with a maximum wall thickness of ≥30 mm but there are few data in patients with extreme hypertrophy (≥35 mm).</td>
</tr>
<tr>
<td><strong>Family history of sudden cardiac death at a young age</strong></td>
<td>• While definitions vary, a family history of SCD is usually considered clinically significant when one or more first-degree relatives have died suddenly aged &lt;40 years with or without a diagnosis of HCM, or when SCD has occurred in a first-degree relative at any age with an established diagnosis of HCM.</td>
</tr>
<tr>
<td><strong>Syncope</strong></td>
<td>• Syncope is common in patients with HCM but is challenging to assess as it has multiple causes.</td>
</tr>
<tr>
<td></td>
<td>• Non-neurocardiogenic syncope for which there is no explanation after investigation is associated with increased risk of SCD.</td>
</tr>
<tr>
<td></td>
<td>• Episodes within 6 months of evaluation may be more predictive of SCD.</td>
</tr>
<tr>
<td><strong>Left atrial diameter</strong></td>
<td>• Two studies have reported a positive association between LA size and SCD. There are no data on the association between SCD and LA area and volume. Measurement of LA size is also important in assessing the risk of AF (see section 9.4).</td>
</tr>
<tr>
<td><strong>Left ventricular outflow tract obstruction</strong></td>
<td>• A number of studies have reported a significant association with LVOTO and SCD. Several unanswered questions remain, including the prognostic importance of provokable LVOTO and the impact of treatment (medical or invasive) on SCD.</td>
</tr>
<tr>
<td><strong>Exercise blood pressure response</strong></td>
<td>• Approximately one third of adult patients with HCM have an abnormal systolic blood pressure response to exercise characterised by progressive hypotension or a failure to augment the systolic blood pressure that is caused by an inappropriate drop in systemic vascular resistance and a low cardiac output reserve.</td>
</tr>
<tr>
<td></td>
<td>• Various definitions for abnormal blood pressure response in patients with HCM have been reported for the purposes of this guideline an abnormal blood pressure response is defined as a failure to increase systolic pressure by at least 20 mm Hg from rest to peak exercise or a fall of &gt;20 mm Hg from peak pressure.</td>
</tr>
<tr>
<td></td>
<td>• Abnormal exercise blood pressure response is associated with a higher risk of SCD in patients aged ≤40 years, but its prognostic significance in patients &gt;40 years of age is unknown.</td>
</tr>
</tbody>
</table>

HCM = hypertrophic cardiomyopathy; LA = left atrium; LVH = left ventricular hypertrophy; LVOTO = left ventricular outflow tract obstruction; NSVT = non-sustained ventricular tachycardia; SCD = sudden cardiac death; TTE = transthoracic echocardiography.
Flow chart for ICD implantation

- **HCM-Risk SCD Score**
  - LOW-RISK: 5-year risk <4%
    - ICD generally not indicated
  - INTERMEDIATE RISK: 5-year risk ≥4%–<6%
    - ICD may be considered
  - HIGH-RISK: 5-year risk ≥6%
    - ICD should be considered

- **ICD recommended**
  - Additional Risk Factors
    - Late Gadolinium Enhancement
    - Genetics (multiple mutations)
    - Apical aneurysm
    - LVEF <50%
    - Abnormal blood pressure response to exercise

*ICD not recommended unless there other clinical features that are of potential prognostic importance and when the likely benefit is greater than the lifelong risk of complications and the impact of an ICD on lifestyle, socioeconomic status and psychological health.
HCM Risk-SCD Calculator

- **Age**: Age at evaluation
- **Maximum LV wall thickness**: Transthoracic Echocardiographic measurement
- **Left atrial size**: Left atrial diameter determined by M-Mode or 2D echocardiography in the parasternal long axis plane at time of evaluation
- **Max LVOT gradient**: 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 should be determined using the modified Bernoulli equation: Gradient: $4V^2$, where $V$ is the peak aortic outflow velocity
- **Family History of SCD**: History of sudden cardiac death in 1 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)
- **Non-sustained VT**: 3 consecutive ventricular beats at a rate of 120 beats per minute and <30s in duration on Holter monitoring (minimum duration 24 hours) at or prior to evaluation
- **Unexplained syncope**: History of unexplained syncope at or prior to evaluation

<table>
<thead>
<tr>
<th>Risk of SCD at 5 years (%)</th>
</tr>
</thead>
</table>

**ESC recommendation:**

---


Validation of the 2014 European Society of Cardiology Guidelines Risk Prediction Model for the Primary Prevention of Sudden Cardiac Death in Hypertrophic Cardiomyopathy

Pieter A. Vriesendorp, MD; Arend F.L. Schinkel, MD, PhD; Max Liebregts, MD; Dominic A.M.J. Theuns, PhD; Johan van Cleemput, MD, PhD; Folkert J. ten Cate, MD, PhD; Rik Willems, MD, PhD; Michelle Michels, MD, PhD

Figure 1. Time-dependent receiver operating characteristic curves for the risk prediction models of the 2014 European Society of Cardiology (ESC) guidelines (area under the curve [AUC]=0.69), 2003 American College of Cardiology (ACC)/ESC guidelines (AUC=0.55), and 2011 ACC Foundation/American Heart Association guidelines (AUC=0.60), and the reference line (AUC=0.5).

Circ Arrhythm Electrophysiol. 2015;8:829-835
Programmed ventricular stimulation predicts arrhythmic events and survival in hypertrophic cardiomyopathy

Konstantinos A. Gatzoulis a,*,1, Stavros Georgopoulos a,b,1, Christos-Konstantinos Antoniou a,1, Aris Anastasakis a,b,1, Polychronis Dilaveris a,1, Petros Arsenos a,1, Skevos Sideris c,1, Dimitris Tsiachris a,1, Stefanos Archontakis a,1, Elias Sotiropoulos c,1, Artemisia Theopistou a,1, Ioannis Skiadas c,1, Ioannis Kallikazaros c,1, Christodoulou Stefanadis a,1, Dimitrios Tousoulis a,1

Test performance measures.

<table>
<thead>
<tr>
<th>Classification criterion</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHA indication for an ICD</td>
<td>85%</td>
<td>15.8%</td>
<td>9.9%</td>
<td>90.6%</td>
</tr>
<tr>
<td>ESC score ≥ 6%</td>
<td>55%</td>
<td>76.7%</td>
<td>20.8%</td>
<td>93.2%</td>
</tr>
<tr>
<td>PVS inducibility</td>
<td>95%</td>
<td>67.2%</td>
<td>24%</td>
<td>99.2%</td>
</tr>
<tr>
<td>PVS inducible OR ESC score ≥ 6%</td>
<td>100%</td>
<td>49.2%</td>
<td>18.2%</td>
<td>100%</td>
</tr>
<tr>
<td>PVS inducible OR AHA indication for an ICD</td>
<td>100%</td>
<td>8.7%</td>
<td>10.7%</td>
<td>100%</td>
</tr>
</tbody>
</table>
ΗΦΕ στην ΥΜΚ

<table>
<thead>
<tr>
<th>ΠΑΡΑΜΕΤΡΟΣ</th>
<th>ΤΙΜΗ</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΕΥΑΙΣΘΗΣΙΑ</td>
<td>96.4%</td>
</tr>
<tr>
<td>ΕΙΔΙΚΟΤΗΤΑ</td>
<td>66.5%</td>
</tr>
<tr>
<td>ΘΕΤΙΚΗ ΔΙΑΓΝΩΣΤΙΚΗ ΑΞΙΑ</td>
<td>24.5%</td>
</tr>
<tr>
<td>ΑΡΝΗΤΙΚΗ ΔΙΑΓΝΩΣΤΙΚΗ ΑΞΙΑ</td>
<td>99.7%</td>
</tr>
</tbody>
</table>

ΠΡΑΚΤΙΚΑ ΣΤΟ 20% ΤΩΝ ΘΕΤΙΚΩΝ ΗΦΕ ΕΠΕΡΧΕΤΑΙ ΤΟ ΠΚΣ, ΕΝΩ ΕΠΙ ΑΡΝΗΤΙΚΟΥ ΗΦΕ ΧΕΔΟΝ ΕΞΑΣΦΑΛΙΖΕΤΑΙ Ο ΑΣΘΕΝΗΣ ΠΕΡΙ ΜΗ ΕΠΕΛΕΥΣΕΩΣ ΤΟΥ
ΣΥΝΟΨΙΖΟΝΤΑΣ

-- ΑΠΟΦΥΓΗ ΑΝΤΑΓΩΝΙΣΤΙΚΩΝ ΑΘΛΗΜΑΤΩΝ

-- ΣΕ ΑΠΟΤΡΑΠΕΝΤΑ ΑΙΦΝΙΔΙΟ Ή ΣΕ ΑΥΤΟΜΑΤΗ VT: ΕΜΦΥΤΕΥΣΗ ΑΠΙΝΙΔΩΤΗ

-- HCM RISK SCORE ΣΕ >16ΕΤΩΝ ΑΝΑ 2ΕΤΙΑ (CLASS I)

-- ΚΛΙΝΙΚΗ ΚΡΙΣΗ, ΕΞΑΤΟΜΙΚΕΥΣΗ ΑΛΛΑ ΚΑΙ ΣΧΟΛΑΣΤΙΚΗ ΣΥΛΛΟΓΗ ΣΤΟΙΧΕΙΩΝ: ΣΗΜΑΝΤΙΚΑ ΓΙΑ ΤΟ ΠΑΡΟΝ ΚΑΙ ΠΟΛΛΑ ΥΠΟΣΧΟΜΕΝΑ ΓΙΑ ΤΟ ΜΕΛΛΟΝ