Cardiomyopathie Hypertrophique
Interprétation critique du “sudden cardiac death risk calculator”

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Relationships with Industry

- Research funding (grant):
  - Directly to me: no
  - Indirectly to my institution: yes (Genzyme, Shire)
- Consulting/advising fees: no
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- Patents: no with Industry (but patent with Iserm-transfert institution)
- Speaker fees: no
- Advisory board fees: no
Sudden cardiac death in HCM
Introduction on SCD in HCM

- **Rate of SCD in HCM patients:**
  - FU of pts with aborted SCD or sVT/VF: **35-41% at 5 y.**
    - Cecchi et al. JACC 1989 - Elliott et al. JACC 1999
  - Primary prevention: **~1% per year**

- **ICD in HCM patients** (registry 506 pts):
  - Appropriate Therapy in **10,6% per y. secondary prevention**
  - or **3,6% per y. primary prevention**

- **Substrate:** Fibrosis, Myocardial disarray
- **Trigger:** Adrenergic stress, SV tachycardia / bradycardia, Ischemia, Obstruction
- **VT/VF**
**The big 5 risk factors for SCD in HCM**

- **Syncope** (especially if recent < 6 months & if non vaso-vagal)
- **Non sustained Ventricular tachycardia** (Holter-ECG 48h) (especially <30 y.)
- **Abnormal response of BP to exercise** (ΔSystBP < 20-25 mmHg; especially <40-50 y.)
- **Family history of SCD** (<40-50 y. and ≥1-2 cases)
- **Marked LVH on echo** (> 30 mm)

→ **ICD in primary prevention**:
  - if ≥ 1 **RF** (class IIa)  
  - if ≥ 2 **RF**  
    - *French reco HAS 2011*
  - Complex algorythm *US reco 2011*
A new risk calculator for SCD in HCM
A new stratification for SCD in HCM


Multicentric retrospective study, 3675 pts, FU 5.7 y., 7 independant RF

<table>
<thead>
<tr>
<th>Predictor Variable</th>
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<tr>
<td>Age at evaluation.</td>
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<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>
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<tr>
<td>Maximal wall thickness: 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>
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<tr>
<td>Left atrial diameter determined by M-Mode or 2D echocardiography in the parasternal long axis plane.</td>
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<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= 4V^2, where V is the peak aortic outflow velocity.</td>
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<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>
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<tr>
<td>History of unexplained syncope at or prior to evaluation.</td>
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Probability SCD at 5 years = 1 − 0.998^{exp(prognostic index)}
where Prognostic index = [0.15939858 x maximal wall thickness (mm)] − [0.00294271 x maximal wall thickness^2 (mm^2)] + [0.0259082 x left atrial diameter (mm)] + [0.0044613 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)].

→ Absolute risk of SCD at 5 years
On line ESC score (ESC web site)

<table>
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<tr>
<th>Risk of SCD at 5 years (%)</th>
<th><strong>2.85</strong></th>
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<tr>
<td>ESC recommendation</td>
<td>ICD generally not indicated **</td>
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**HCM Risk-SCD Calculator**

- **Age**
  - Years: 20
- **Maximum LV wall thickness**
  - mm: 35
- **Left atrial size**
  - mm: 33
- **Max LVOT gradient**
  - mmHg: 45
- **Family History of SCD**
  - No
  - Yes
- **Non-sustained VT**
  - No
  - Yes
- **Unexplained syncope**
  - No
  - Yes

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Trans-thoracic Echocardiographic measurement

Left atrial diameter determined by M-Mode or 2D echocardiography in the parasternal long axis plane at time of evaluation.

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: \( \text{Gradient} = 4V^2 \), where \( V \) is the peak aortic outflow velocity.

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).

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.

History of unexplained syncope at or prior to evaluation.

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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.

Limitations of current ESC prediction of SCD in HCM / indication for ICD
1. Situations for which risk stratification is not appropriate

- New risk stratification not appropriate for particular etiologies (non sarcomeric HCM)
- not appropriate for young patients (<16 years)
- not validated after myectomy / alcohol ablation
- should be used cautiously in pts with MWT ≥35 mm
2. Based on retrospective data with potential bias

- Multi center study: possible heterogeneous evaluation of patients (ex: assessment of family history? Valsalva systematic or not?)
- Does not consider one major RF: Abnormal BP during exercise
- 21% of patients had at least 1 RF not evaluated (out of the 7 RF)
- Period of inclusion? Probably quite old
- Population from 6 referral centers in Europe
3. Empiric estimation of threshold for ICD implantation

- For every 16 ICD implantations in pts with risk $\geq 4\%$ at 5 years, 1 patient can potentially be saved from SCD at 5 years (5-year SCD risk of $\geq 4\%$ identified 71% of SCD endpoints with 30% ICD implants in pts without SCD at 5 years)

  O’Mahony EHJ 2014

- A more conservative threshold proposed by ESC 2014: ICD in pts with risk $\geq 6\%$ at 5 years, but no precise rationale

  Elliott EHJ 2014
4. A modest improvement of risk prediction?

- **Prediction of the new model:** C-index was 0.70 (95% CI: 0.68-0.72) and **external validation** C-index: 0.67 (95% CI: 0.64-0.70); versus a C-index of 0.54 (95% CI: 0.51-0.56) with four conventional RF (and C-index 0.63-0.64 with conventional 5 RF)

  O’Mahony EHJ 2014 & O’Mahony Heart 2012

- **Poor prediction of SCD in a retrospective US cohort** of 1629 pts: 35 SCD events, but only 4 of these (11%) had high predictive risk scores >6%/5 years, and most (60%; n = 21) had scores <4%/5 years that would not justify ICDs.

  Maron BJ et al. Am J Cardiol 2015 Sep 1;116(5):757
5. Side effects of ICD not taken into account and no medico-economic evaluation

- **Effet indésirables nombreux** (hématome, épanchement péricardique, infection de loge ou de sonde, chocs électriques inappropriés: 27 % des patients versus 20 % chocs appropriés, impact psychologique et qualité de vie)

- **Taux de complications** sévères du DAI chez 2190 patients CMH (méta-analyse): 3,4 % par an et taux de choc inapproprié: 4,8 % par an

  Schinkle et al. Circ Heart Fail 2012;5(5):552

- **Pas d’étude de ratio coût-efficacité acceptable pour la collectivité:** balance entre coûts du défibrillateur (seul environ 13000 €, tarif des GHS correspondant 05C191-2-3 :16000 à 23000 €), son suivi, la prise en charge des complications versus le gain en terme de survie.
6. Additional risk factors probably useful

- MRI in 217 HCM pts, LE in 63% pts
- LE predictive of global composite end-point (CV morbi mortality), HR: 3.4; p=0.006
- LE non predictive of composite end-point for “arhythmia” after multivariate (but univariate, HR: 1.30; p=0.014)

O’Hanlon JACC 2010;56:867

- SCD more important in TNNT2 families vs MYBPC3 families
- Poor prognosis in HCM pts with sarcomeric mutation vs non-sarcomeric mutation (unknown cause)
  Olivotto I, Mayo Clin Proc 2008;83:630
- Poor prognosis in patients with multiple mutations
Perspective for improvement of SCD prediction / ICD indication

Étude DEFICARD

- Analyse de la prédiction de la mort subite & des choix d’implantation de défibrillateur automatique dans la CMH
- Etude prospective nationale, inclusion 2000 patients en France, suivi 4 ans
- Analyse multivariée des FDR & analyse médico-économique (ICER, coût/efficacité, coût/utilité)
- Critères secondaires d’évaluation: IRM & Génétique
- AAP PRME 2015, Ph Charron
Conclusions

« Medicine is a science of uncertainty and an art of probability »
William Osler 1849-1919

✓ Significant progress were made for risk stratification for SCD in HCM

✓ Threshold for ICD implantation (primary prevention) are not well established but some proposed by 2014 ESC Guidelines

✓ We still need to progress and identify additional RF, that need to be validated in large cohort of patients with prospective FU and multivariate analyses