Prevention of Sudden Cardiac Death in Hypertrophic Cardiomyopathy

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- Hypertrophic cardiomyopathy (HCM) is a genetically heterogeneous heart muscle disorder characterized by myocardial hypertrophy in the absence of abnormal loading conditions .
- HCM is the most common inherited cardiovascular disorder, affecting 1 in 500 individuals worldwide
- It is a leading cause of sudden cardiac death (SCD) in young adults.

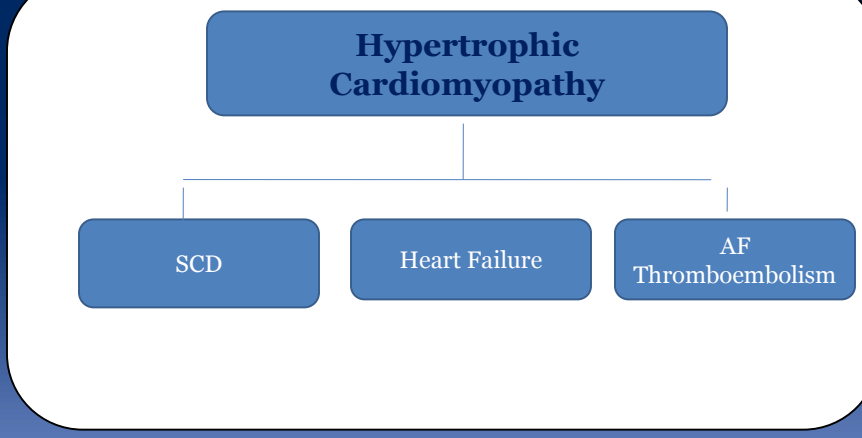
Overview

- Size of the problem
- Causes of sudden cardiac death
- Identifying those at risk
- Managing risk
- Paediatric Age group
- Sport and SCD

Size of the problem

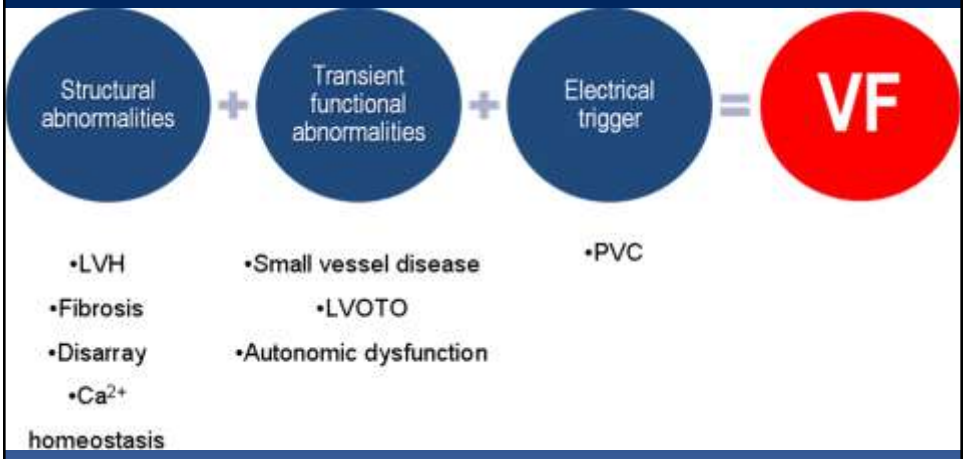
- Data from contemporary studies suggest that the overall risk is relatively small with annual sudden cardiac death (SCD) rates of 1% or less in most series peaking in early adulthood.

Causes of cardiac death



- Data from chance ECG recordings and stored intracardiac EGMs from ICDs suggest that SCD in HCM is most commonly caused by VF.
- Numerous cardiac arrhythmias have been reported in association with SCD in HCM, including asystole, atrioventricular block, pulseless electrical activity, and supraventricular arrhythmias.

A model for SCD in HCM



A model for SCD in HCM, modified from Myerburg et al (Am J Cardiol 1989;63:1512–16).

- The challenge for clinicians is to identify the small cohort of patients who are at risk in order to target potentially lifesaving therapy with implantable cardioverter defibrillators (ICD).

Identifying the High Risk Patients

Risk Assessment

- Clinical and family history
- 48-hour ambulatory ECG
- TTE
- CMR in the case of poor echo windows.
- A symptom-limited exercise test

Table 7 Major clinical features associated with an increased risk of sudden cardiac death in adults

Risk Factor	Comment
Age	• 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 syncope.
Non-sustained ventricular tachycardia	• NSVT (defined as ≥3 consecutive ventricular beats at ≥120 BPM lasting <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.
Maximum left ventricular wall thickness	• 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).
Family history of sudden cardiac death at a young age	• While definitions vary, a family history of SCD is usually considered clinically significant when one or more first-degree relatives have died suddenly aged <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.
Syncope	• Syncope is common in patients with HCM but is challenging to assess as it has multiple causes. • Non-neurocardiogenic syncope for which there is no explanation after investigation is associated with increased risk of SCD. • Episodes within 6 months of evaluation may be more predictive of SCD.
Left atrial diameter	• 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).
Left ventricular outflow tract obstruction	• A number of studies have reported a significant association with LVOTO and SCD. Several unanswered questions remain, including the prognostic importance of provocable LVOTO and the impact of treatment (medical or invasive) on SCD.
Exercise blood pressure response	• 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. • 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 >20 mm Hg from peak pressure. • Abnormal exercise blood pressure response is associated with a higher risk of SCD in patients aged ≤40 years, but its prognostic significance in patients >40 years of age is unknown.

NSVT

- Asymptomatic nonsustained ventricular tachycardia (NSVT), at a rate between 120 and 200 beats per minute (BPM), occurs in 25% of adults with HCM.
- NSVT in patients aged ≤30 years is associated with a fourfold increase in the risk of SCD, but there is no significant association in older patients.

Left ventricular hypertrophy

- Severe LVH (maximum wall thickness (MWT) ≥30 mm) is associated with SCD.
- **Limitations**

➢ poor echocardiographic windows.

➢ The thickness of a single myocardial segment may not adequately represent the true burden of hypertrophy—for example, a patient with isolated apical hypertrophy of 20 mm is considered to have the same risk as a patient with 20 mm LVH in all myocardial segments

Exercise blood pressure reponse

- ABPRE is characterized by progressive hypotension or a failure to augment the systolic blood pressure.
- ABPRE should be assessed during a maximal symptom limited protocol and in the absence of any medication which can potentially modify the haemodynamic response.
- ABPRE is associated with SCD in patients ≤40 years, but is not an independent predictor in multivariable analyses.
- The prognostic significance of ABPRE in patients >40 years has not been examined.

Combination of major risk factors

- Several studies investigated the risk of SCD in the presence of combinations of major risk factors.
- Patients with two or more risk factors (12%) had an estimated annual SCD risk of 4–5%.

Possible Risk Factors

- Atrial fibrillation
- Myocardial Ischemia
- Left ventricular outflow tract obstruction
- Genotype
- Late gadolinium enhancement in CMR
- Physical exertion
- Fractionation of paced right ventricular electrograms
- Left ventricular apical aneurysms

Genotype

- Patients with a sarcomere protein gene mutation present earlier and report a higher prevalence of family history of HCM and SCD than those without a mutation.

- In families with a *TNNT2* gene mutation, SCD can also occur at a younger age, even before ventricular hypertrophy is present.
- More recently, systematic genotyping revealed patients with two mutations in the same gene or in different genes, who have a more severe phenotype with a younger age of onset and more adverse events.

- However, all of these studies had the same limitations: small population size, low prevalence of each mutation, intra- and inter-familial variability in expression of the phenotype, and have been contradicted in more recent studies.

Physical Exertion

- Few studies evaluated this possible risk factor.
- Three studies reported on the circumstances preceding death. In two studies, about two-thirds of SCD occurred during exertion (32–44% during mild exertion and 22–32% during moderate to severe exertion).

- Exercise induced ventricular arrhythmia, present in ~2% of patients, is also independently associated with a threefold increase in SCD risk.

Models for estimating sudden cardiac death risk

- Utilizing the major risk factors to estimate risk and to guide ICD therapy has a number of limitations: it estimates relative—and not absolute—risk; it does not account for the different effect size of individual risk.
- Consequently, current risk algorithm discriminate modestly between high- and low-risk patients

- Moreover, some risk factors such as hypertrophy are considered as binary variables when in fact they are associated with a continuous increase in SCD risk.
- As a result, existing algorithms have a low positive predictive accuracy for SCD that results in the unnecessary treatment of patients who are at intrinsically low risk

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FASTTRACK CLINICAL RESEARCH
Myocardial disease

A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM Risk-SCD)

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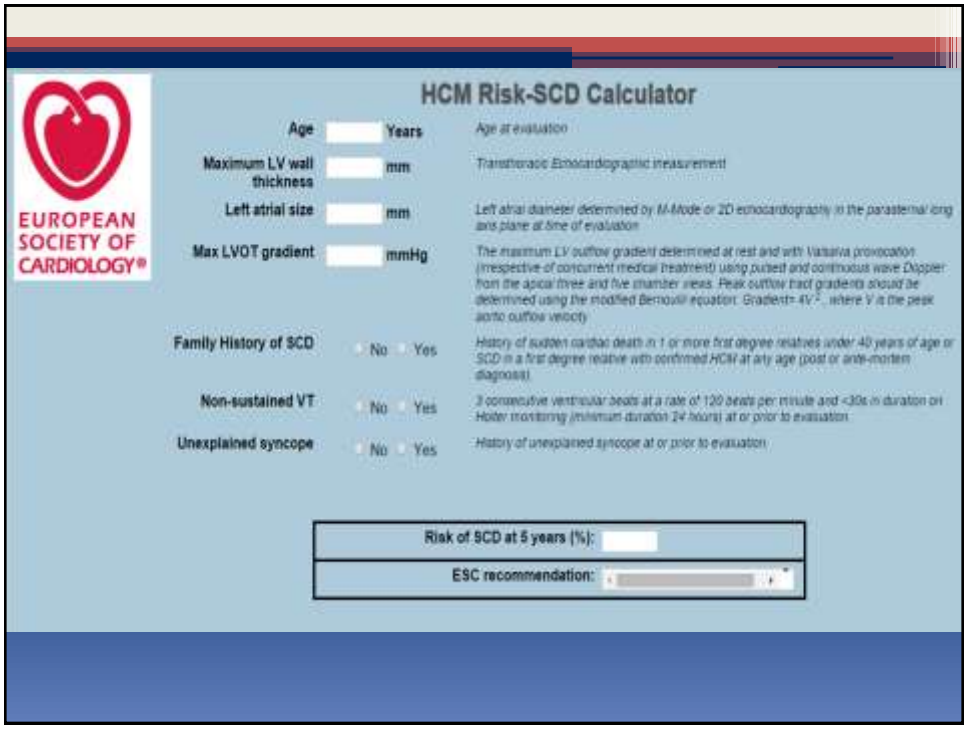
- A multicentre, retrospective, longitudinal cohort study of 3675 patients—known as HCM Risk-SCD—developed and validated a new SCD risk prediction model.
- HCM Risk-SCD uses predictor variables that have been associated with an increased risk of SCD in at least one published multivariable analysis

- This excludes abnormal blood pressure response as a risk marker.
- The model provides individualized 5-year risk estimates.

HCM Risk-SCD is recommended as a method of estimating risk of sudden death at 5 years in patients aged ≥16 years without a history of resuscitated VT/VF or spontaneous sustained VT causing syncope or haemodynamic compromise.	I	B



Managing Risk

Prevention of Sudden Cardiac Death

Exercise Restriction

- International guidelines recommend that HCM patients should be excluded from competitive sports and discouraged from intense physical activity.
- The exact mechanisms by which physical exertion precipitates SCD is not known, but probably include exercise induced hypotension, LVOTO, and myocardial ischaemia.

Antiarrhythmics

- There are no data to support the use of antiarrhythmic agents for the prevention of SCD in HCM.

- ***Amiodarone*** increases the threshold for VF and in one small observational study reduced SCD in HCM patients with NSVT on Holter monitoring.
- However, observational data suggest that amiodarone often fails to prevent SCD.

- ***Disopyramide***, frequently used for the treatment of symptomatic LVOTO, does not appear to have a significant impact on SCD

Implantable cardioverter defibrillators

- Survivors of VF or sustained ventricular tachycardia are at very high risk of subsequent lethal cardiac arrhythmias and should all receive an ICD for secondary prevention.

ICD implantation is recommended in patients who have survived a cardiac arrest due to VT or VF, or who have spontaneous sustained VT causing syncope or haemodynamic compromise, and have a life expectancy of >1 year.	I	B

- As the majority of HCM patients do not have a prior history of cardiac arrest, identification of individuals at high risk of SCD who would benefit from a primary prevention ICD remains a challenge

- Recommendations are instead based on observational, retrospective cohort studies that have determined the relationship between clinical characteristics and prognosis.
- There are no randomized trials or statistically validated prospective prediction models that can be used to guide ICD implantation in patients with HCM.

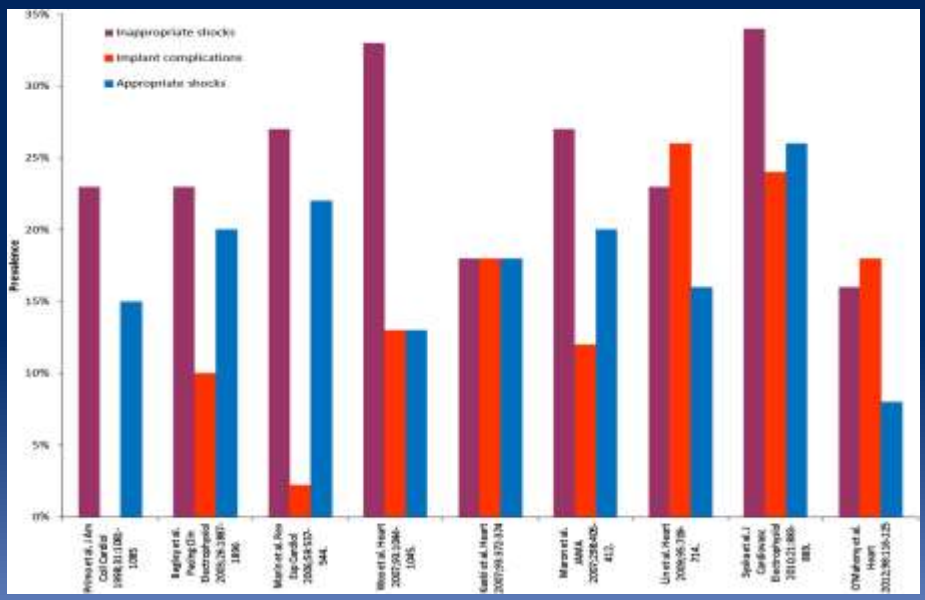
Table 1 The 2003 ACC/ESC and 2011 ACCF/AHA guidelines

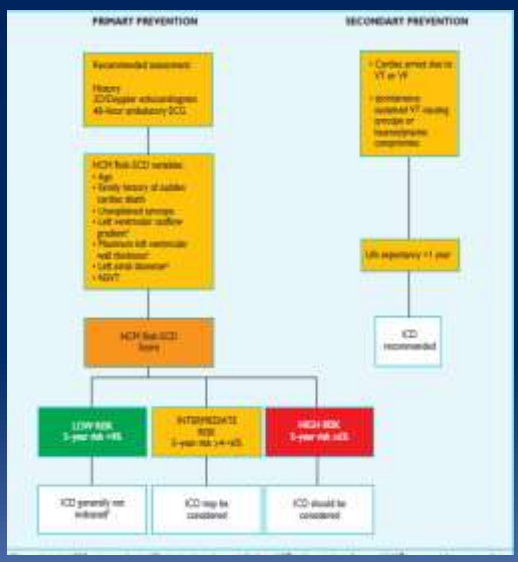
	2003 ACC/ESC guidelines	2011 ACCF/AHA guidelines
Assessment		▶ Non-sustained ventricular tachycardia ▶ Blood pressure response to exercise ▶ Unexplained syncope ▶ Family history of sudden cardiac death ▶ Maximal wall thickness ▶ Other modifiers/risk factors
Recommendation		No risk factors: *ICD not recommended*
	Single risk factor: *Consider ICD*	Recent syncope, or maximal wall thickness >30 mm or family history of sudden cardiac death: *ICD reasonable*
	Multiple risk factors: *ICD implantation*	Non-sustained ventricular tachycardia or abnormal blood pressure response to exercise with other risk factors or modifiers: *ICD can be useful* Non-sustained ventricular tachycardia or abnormal blood pressure response to exercise in isolation: *ICD uncertain*

ACC, American College of Cardiology; ACCF, American College of Cardiology Foundation; AHA, American Heart Association; ESC, European Society of Cardiology; ICD, implantable cardioverter defibrillator.

- Importantly, the ACCF/AHA guidelines consider NSVT and ABPRE as clinically important only when they occur in the presence of other risk factors.

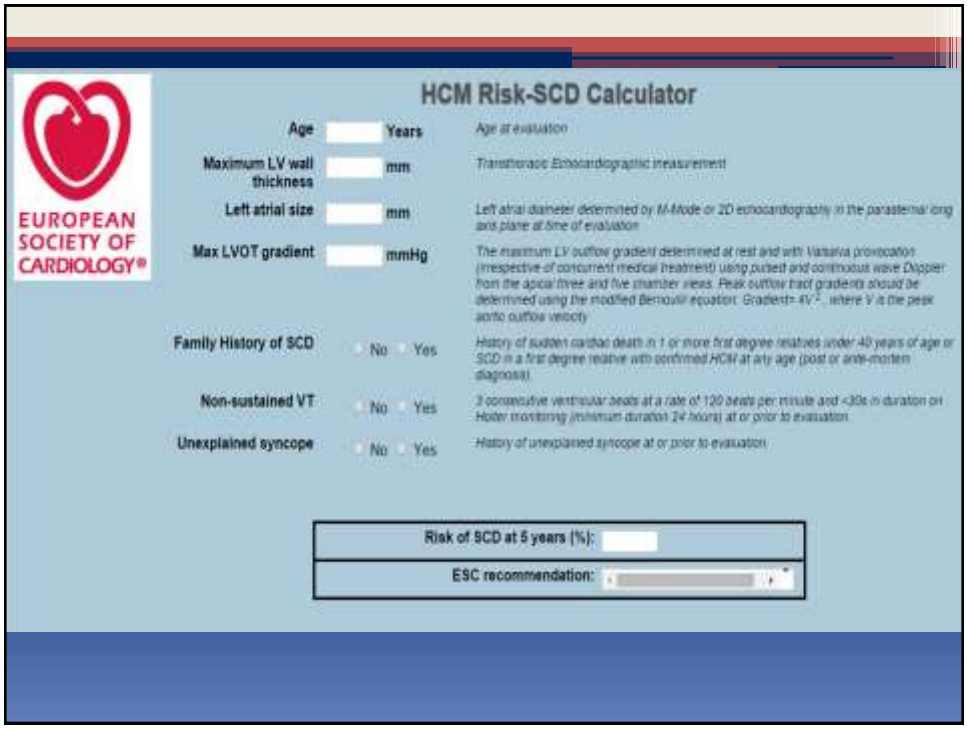
Implant complications, inappropriate and appropriate shocks in HCM





ICD therapy 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.



- HCM Risk-SCD should not be used in patients <16 years of age, elite athletes or in individuals with metabolic/infiltrative diseases (e.g. Anderson-Fabry disease) and syndromes (e.g. Noonan syndrome).
- The model does not use exercise-induced LV outflow tract gradients and has not been validated before and after myectomy or alcohol septal ablation.

- As the relationship between maximum LVwall thickness and risk is non-linear, the calculated risk for SCD falls in patients with severe LVH (≥35 mm).
- HCM-RISK should be used cautiously in patients with a maximum left ventricular wall thickness ≥35 mm.

Risk of sudden death in children

- The definition of severe hypertrophy in infants, children and pre-adolescents has been defined as a maximum LV wall thickness ≥30 mm or a Z-score ≥6 is considered to be a major risk factor in children.
- Implantation of an ICD (epicardial if necessary) is indicated after a life-threatening ventricular arrhythmia in children

- Implantation of an ICD should be considered in children who have two or more major risk factors. (class II a/C)
- Single-chamber defibrillators suffice in the majority of cases.
- In individual patients with a single risk factor,ICD implantation may be considered after careful consideration of the risks and benefits to the child and family (class IIb/C)

- It is important to stress that all guidelines recommend the individualisation of treatment and suggest the assessment of other variables such as LVOTO when evaluating risk.

Care Beyond SCD Prevention

HCM patients treated with an ICD are effectively protected from SCD, but are not immune to other HCM related complications such as heart failure and systemic embolisation.

ICD recipients should be followed up regularly to monitor symptoms, as well as device complications.

In patients who develop AF, anticoagulation should always be considered.

Take Home Message

- Ventricular fibrillation is the most common cause of SCD in HCM.
- SCD can be prevented by implantable cardioverter defibrillator (ICD) therapy.
- Every HCM patient should undergo a comprehensive assessment of SCD risk factors (NSVT, FH of SCD, unexplained syncope, ABPRE, and maximal wall thickness assessment).

- ICD therapy should be offered to those with multiple risk factors of SCD.
- Patients with no risk factors should be reassured and regularly reassessed.
- Patients with a single risk factor have a good overall prognosis, but ICD therapy can be useful in a minority.

- Current risk stratification algorithms are limited and only a minority of ICD recipients receive appropriate shock therapy.
- ICD recipients have a high risk of developing implant complications and receiving inappropriate shocks.
- There is a clear need for an SCD risk prediction model which provides individualised SCD risk estimates.