Prevention of sudden death in hypertrophic cardiomyopathy: bridging the gaps in knowledge

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Sudden cardiac death (SCD) is the most devastating complication of hypertrophic cardiomyopathy (HCM). Although the annual rate of SCD in the general HCM population is < 1% per year according to contemporary series, there is still a small subset of patients who are at increased risk of SCD. The greatest challenge in the management of HCM is identifying those at increased risk as an implantable cardioverter defibrillator (ICD) is a potentially life-saving therapy. In this review, we sought to summarize the available data on SCD in HCM and provide a clinical perspective on the current differing and somewhat conflicting European and American recommendations on risk stratification, with balanced guidance with regards to rational clinical decision making. Additionally, we sought to learn more on the actual implementation of the guidelines by HCM experts worldwide.

Keywords
Hypertrophic cardiomyopathy • Sudden cardiac death • Risk Stratification • Implantable cardioverter defibrillator

Introduction

Sudden cardiac death (SCD) is the most devastating complication of hypertrophic cardiomyopathy (HCM). Although the annual rate of SCD in the general HCM population is < 1% per year according to contemporary series, there is still a small subset of patients who are at increased risk of SCD. The greatest challenge in the management of HCM is identifying those at increased risk as an implantable cardioverter defibrillator (ICD) is a potentially life-saving therapy. In this review, we sought to summarize the available data on SCD in HCM and provide a clinical perspective on the current differing and somewhat conflicting European and American College of Cardiology Foundation/American Heart Association (ACCF/AHA) recommendations on risk stratification, with balanced guidance with regards to rational clinical decision making. Additionally, we sought to learn more on the actual implementation of the guidelines by HCM experts worldwide.

Pathophysiology of hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy is an autosomal dominant disorder with both a wide spectrum of disease expression and variable penetrance. Although the exact mechanisms for SCD remain incompletely understood as yet, underlying abnormalities of myocardial architecture are thought to play a role in both arrhythmogenesis and left ventricular (LV) remodelling. Autopsy observations have demonstrated a range of histopathologic features, which can be grouped into three distinct features, namely extensive disarray of myocytes and myofibrils, abnormalities of the intramural microvasculature, and interstitial fibrosis. Disorganized myocardial architecture comprises hypertrophied myocytes with bizarre shapes, multiple abnormal myocardial connections, and chaotic alignment. Cellular disarray is patchy and widely distributed and not solely limited to areas of myocardial hypertrophy, and has been shown to be more extensive in young patients who die of their disease. Abnormalities of the myocardial microvasculature are characterized not only by a reduction in arteriolar density but also by small vessel dysplasia, a term often referred to as SICAD (Small Intramural Coronary Artery Dysplasia). Intimal and/or medial thickening, in addition to proliferation and disorganization of smooth muscle cells, ultimately result in a reduction in luminal cross-sectional area, further aggravated by dense perivascular collagen and increased medial collagen content. Myocardial fibrosis is seen commonly in patients with HCM and may present as varying degrees of both replacement

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Prevalence of sudden cardiac death in hypertrophic cardiomyopathy

The true prevalence of SCD in HCM is difficult to estimate, as a substantial portion of cases remain unrecognized. Early studies evaluating this issue demonstrated alarmingly high rates of SCD reaching up to 6% per year.\(^\text{10–12}\) Indeed, the most common mode of death was sudden in some of these early reports.\(^\text{10}\) However, these studies originated from tertiary centres and hence were subject to considerable referral bias. With increased awareness of the disease, improvement in diagnostic methods, and dissemination of family screening programmes, lower risk patients have gradually become included into HCM cohort studies. More contemporary studies performed after the introduction of life-saving therapies as ICD, demonstrate a much lower annual SCD rate of \(<1\%\).\(^\text{1–4}\)

Though HCM is more frequently diagnosed in males, the risk of SCD seems to be similar in men and in women.\(^\text{13}\) Similarly, there is no direct evidence associating race and risk of SCD.

Conventional risk factors

Sudden cardiac death may be the first presentation of the disease in patients with HCM, and remains the most feared complication. A major challenge in the management of HCM lies in the ability to identify the minority of patients at high risk and provide reassurance to those deemed to be at low risk for sudden death. Although there are several established risk factors for SCD and progression to heart failure, these markers individually have low-positive predictive value. Yet, the negative predictive value in the absence of any risk factors is high.

Thus, the risk factor profile for any individual patient is more accurately assessed in terms of their total burden of risk as opposed to the presence or absence of individual markers of risk alone (Figure 1).

Prior personal history of ventricular fibrillation, aborted sudden cardiac death, or sustained ventricular tachycardia

Those patients who have previously experienced a high-grade, potentially fatal arrhythmia are at highest risk for further arrhythmic events, with an annual event rate in the range of 10% per year. However, even this group of particularly high-risk patients may experience no further recurrence or prolonged event-free intervals between arrhythmic episodes.\(^\text{14}\)

Family history of sudden cardiac death

While it has been recognized that SCD events can cluster in families, there are somewhat conflicting data regarding the link between a family history of SCD and risk for any individual patient. This is likely related to differences in the definition of familial SCD in the various studies. Notably, most studies have used as age cut-off 40–50 years

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**Figure 1** The risk model pyramid for SCD in HCM.
and have considered only first-degree relatives. Several studies have been unable to demonstrate a significant relationship between family history of SCD and SCD on multivariable analysis, whereas a recent meta-analysis has demonstrated an independent but weak correlation, with an average reported hazard ratio of 1.27 (95% confidence interval, CI: 1.16–1.38).

Syncope
Syncope occurs in ~15–25% of patients with HCM, with the principal causes being broadly divided into two mechanistic categories: (i) arrhythmic causes (both brady- and tachyarrhythmias) and (ii) primary haemodynamic abnormalities such as left ventricular outflow tract obstruction (LVOTO) and abnormal vascular control mechanisms. Given the multifactorial aetiologies for syncope, a thorough clinical history is required before it can be considered a potential marker for sudden death. The most compelling data relating unexplained syncope with increased risk of sudden death comes from a large consecutive series of 1511 patients. In this cohort, the relative risk of SCD was 1.78 in those patients with a history of recurrent syncope compared with patients without such a history. This association held true only when syncope had occurred within the preceding 6 months. In patients with a remote history of syncope (> 5 years prior to the clinical visit), no independent association with SCD could be demonstrated.

Non-sustained ventricular tachycardia
Although the definition of NSVT is not uniform in all studies, in most it is defined as ≥3 consecutive beats but <30 s duration at a rate of ≥120 beats/min. Non-sustained ventricular tachycardia has been demonstrated to be associated with increased risk of SCD, particularly in those patients younger than 30 years of age, with an averaged HR of 2.89 [95% CI: 2.21–3.58]. Nevertheless, the high prevalence of NSVT in patients with HCM (17–32%) limits its use as a single risk marker for sudden death. Like other risk markers, NSVT is not a binary variable but a spectrum. As only a minority of patients have frequent, fast, or relatively prolonged episodes of NSVT, many experts rely on these factors for decision making regarding ICD implantation. However, there is very little evidence to suggest that the rate, duration, or frequency of runs of NSVT influences its prognostic significance. While exercise-induced ventricular arrhythmias have been shown to be markedly rare in a large series of patients with HCM, occurring in only 2% of a total of 1380 patients studied, the presence of NSVT or ventricular fibrillation on exercise is associated with a significantly increased risk of sudden death or AICD discharge.

Maximal left ventricular wall thickness
An association between absolute LV wall thickness and risk of SCD has been clearly documented in a number of large studies, with a LV wall thickness ≥30 mm being shown as a risk factor of SCD. In a study of 500 patients, the authors demonstrated an increase in risk of sudden death in direct relation to an increase in LV wall thickness. Patients with a wall thickness >30 mm had a substantial long-term risk of sudden death of 20% at 10 years and 40% at 20 years. It is important to recognize that risk does not automatically increase when wall thickness reaches a threshold of 30 mm, but increases in a linear fashion, and is of more prognostic significance in the younger patient.

Abnormal blood pressure response to exercise
An ABPR is present in up to one-third of patients with HCM. It is noted more often in younger patients, and in those with a family history of HCM or sudden death. Possible mechanisms for ABPR include LVOTO leading to a fall in cardiac output, inadequate diastolic filling time at high heart rates leading to a fall in stroke volume, and a fall in systemic vascular resistance due to inappropriate vasodilatation. The presence of ABPR has been associated with an increased risk of sudden death in patients below the age of 50 years (with an odds ratio of 4.5 in one study), albeit with a very low predictive positive value of 14–15%. However, the high negative predictive value of 95–97% means that its absence is potentially useful in reassuring the patient in the absence of any other risk factors for SCD.

Modifying factors
Conventional risk factors identify many patients at high risk of SCD, yet most episodes of SCD occur in patients without conventional risk factors. This has led to the search for new markers of susceptibility.

Genetics
The genetic basis of HCM in many patients brought with it the hope of being able to identify ‘malignant’ mutations through genotype–phenotype correlation studies, which would enable the early detection of patients at high risk of SCD in the absence of or prior to the development of other conventional risk factors. However, this strategy was significantly limited by the variability in penetrance and phenotypic expression seen within individual families with the same sarcomeric mutation. Several studies found a correlation between five mutations (four in the MYH7 gene and one in cardiac troponin T) and a high incidence of SCD and hence considered these as ‘malignant’. Notably, the studies on these mutations included a limited number of families. Furthermore, these associations were inconsistent with findings from other studies. Ackerman et al. found that only 1% of 293 unrelated HCM patients screened at the Mayo clinic possessed one of the five ‘malignant’ mutations. Given that no clear genotype–phenotype correlations have been demonstrated, the use of genotyping alone as a risk-stratifying tool is of very limited use.

A number of studies have found a 5% occurrence rate for the presence of more than one disease-causing mutation in patients with HCM. Several small studies have found that patients with homozygous mutation and with double or compound heterozygous sarcomere mutations have a more severe form of HCM compared with patients with a single mutation.
usually present at a younger age and exhibit more extensive hypertrophy. Additionally, heart failure and SCD are significantly more common among this cohort compared with individuals, who carry a single mutation. Moreover, a recent study showed that the presence of multiple rare variants in sarcomere genes was associated with increased risk of SCD. In contrast, our unpublished data on 1100 probands do not support the gene dosage theory. All of these studies are to some extent limited by the low SCD event rates in most contemporary HCM cohorts. Given the lack of well-established genotype–phenotype correlations, genetic testing is not currently recommended in most cases as part of risk stratification for SCD. However, the presence of multiple mutations, which appear to confer a higher risk for SCD, may serve as a risk modifier in determining the need for ICD implantation for primary prevention, but requires confirmatory studies.

Late gadolinium enhancement on cardiac magnetic resonance imaging

The substrate for potentially life-threatening ventricular arrhythmias in HCM is believed to be myocardial fibrosis resulting from bursts of silent and recurrent microvascular ischemia. The use of contrast cardiac magnetic resonance (CMR) imaging with late gadolinium enhancement (LGE) has enabled us to identify and quantify myocardial fibrosis in a non-invasive way. The histological basis of LGE in HCM has traditionally been difficult to assess, but we have previously demonstrated a strong correlation between the extent of myocardial fibrosis in LV myocardium obtained from septal myectomy (as assessed by histologic examination) and LGE (as determined from contrast-enhanced CMR studies performed prior to myectomy). Of note, regions of late enhancement can represent partial rather than complete replacement fibrosis. The amount of LGE can be quantified as a percentage of the total LV mass. About two-thirds of patients with HCM display areas of LGE in varying degrees of extent and location. The two major distribution patterns of LGE are intramural, within the hypertrophied segments, presumed to correspond to replacement fibrosis, and hinge (right ventricular insertion) points, presumed to correspond to interstitial fibrosis, and/or myocyte disarray. Several studies have demonstrated a strong association between the presence of LGE and NSVT on ambulatory Holter monitoring. As NSVT is an independent predictor of SCD, this has led to the investigation of the relationship between LGE and SCD, and its potential role as a novel risk factor. While most studies have found LGE to be a univariate predictor of SCD, findings regarding LGE as an independent predictor for SCD are inconsistent. In a recent large, multicentre study of 1293 patients, LGE has emerged as an independent predictor for SCD, where there was a continuous relationship between the extent of LGE and the risk of SCD. A substantial extent of myocardial fibrosis (≥15% of total LV mass) was associated with a two-fold increase in SCD at 5 years compared with patients with no LGE. In contrast, a study by Ismail et al. on 711 patients who were followed for a median of 3.5 years found the amount of LGE to be significantly associated with SCD on univariable regression. However, the association did not remain statistically significant after adjustment for LV ejection fraction.

A recent meta-analysis of six clinical studies has shown that LGE is significantly correlated with increased risk of SCD in low-risk patients according to the conventional risk factors. Notably only the presence, but not the extent of LGE, was significantly related to the risk of SCD. A recent study showed that hinge LGE is not a determinant of SCD risk. Interestingly, the spatial distribution of LGE significantly correlated with depolarizing and repolarizing electrical abnormalities in high-risk patients with malignant ventricular arrhythmia.

Apical aneurysm

Apical aneurysm is a rare complication of HCM, which usually occurs when the hypertrophy involves predominantly the apex of the LV. The largest series to date by Maron et al found a prevalence of 2.2% in the general HCM population. A more recent study identified apical aneurysm in 18.3% of patients with apical HCM. Apical aneurysm has been associated with a higher rate of adverse cardiovascular events compared with the general HCM population with an annual event rate of 10.5% per year including sudden death, appropriate ICD discharges, non-fatal thromboembolic stroke, and progressive heart failure and death. Furthermore, patients with a large apical aneurysm (>4 cm) were more likely to experience an adverse event. Most aneurysms have a scarred rim, which is commonly associated with extensive areas of myocardial fibrosis. This likely represents an arrhythmogenic substrate for malignant ventricular tachyarrhythmia. More than 40% of patients with apical aneurysm exhibited bursts of non-sustained monomorphic VT on Holter monitoring. The mechanism responsible for the formation of apical aneurysm in HCM is most probably supply/demand mismatch.

Left ventricular outflow obstruction

Left ventricular outflow gradient ≥30 mmHg at rest has been associated with increased risk of SCD. Maron et al. showed that the probability of SCD was significantly greater among patients with LVOTO than patients without (relative risk of 2.1). However, the absolute difference in the annual rate of SCD between patients with and without LVOTO was small (1.5% vs. 0.9%). Left ventricular outflow tract obstruction had a high-negative predictive value at 95% but a low-positive predictive value at 7%. The magnitude of LVOTO was not associated with the risk of SCD. Elliott et al. also found a significant association between LVOTO and risk of SCD or appropriate ICD discharge. Left ventricular outflow tract obstruction was an independent predictor of SCD (relative risk of 2.4); however, the annual rate of SCD in patients with LVOTO and no other conventional risk factors was very low (0.39% per year). Again, LVOTO had a high-negative predictive value and a low-positive predictive value for SCD at 95.9% and 9.7%, respectively. In contrast to the former study, they demonstrated a significant correlation between the severity of the obstruction and the risk of SCD. A number of papers demonstrated the beneficial effect of abolishment of LVOTO by septal myectomy, with a significant decrease in the appropriate ICD discharge rate and risk for SCD post-operatively. Nevertheless, a study on 649 patients with resting obstructive HCM demonstrated that medically treated mildly symptomatic patients with obstructive HCM had similar overall and HCM-related survival to patients treated invasively. Of note, unlike the aforementioned studies, a recent study on 293 patients found that non-obstructive HCM was associated with...
significantly higher rates of ventricular arrhythmia than labile obstruction and similar to obstructive HCM despite a similar mean number of conventional risk factors for SCD. Notably, the low absolute risk reduction resulting from LVOT gradient reduction does not warrant treatment strategies to reduce LVOT in an otherwise asymptomatic patient.

### Age
Initial reports showed that SCD almost exclusively occurred in patients younger than 35 years of age. Additionally, a recent study on 428 HCM patients at ≥60 years of age, found that the risk for SCD in patients with HCM surviving into the seventh decade of life was low even in the presence of conventional risk factors. Nonetheless, an international, multi-centre study on 744 largely unselected patients with HCM has found that although SCD is more common among younger patients it is not confined to this group of patients and continue to occur throughout life (20% of SCD in patients older than 65 years of age).

### Left ventricular systolic dysfunction
End-stage HCM, which is characterized by systolic dysfunction (i.e. ejection fraction <50%) is uncommon. A study on 1259 HCM patients found the frequency of end-stage HCM to be 3.5%. The study observed an appropriate ICD intervention rate of 10% PER year, similar to that reported in HCM patients with ICD implanted for secondary prevention. The authors suggested that end-stage HCM be considered as a risk factor for SCD. Indeed, end-stage HCM is a class IIb indication for prophylactic ICD implantation in the absence of other risk factors for SCD according to the ACCF/AHA guidelines. It is noteworthy that no study of an unselected HCM cohort has examined the value of systolic LV ejection fraction as a predictor of SCD.

### Left atrial diameter
Spirito et al. found that left atrial size, as assessed by M-mode echocardiogram, was independently associated with sudden death on multivariable survival analysis. The Hypertrophic Cardiomyopathy Outcomes Investigators also reported left atrial diameter to be an independent predictor of SCD and have therefore incorporated it into the clinical risk prediction model.

### Exercise
Participation in high-intensity competitive sports may itself induce arrhythmia and serve as a modifiable risk factor for SCD, even in the absence of conventional risk factors. As such, current guidelines advise patients with HCM against participation in competitive sports with the exception of those of low intensity. Notably, while the European Society of Cardiology (ESC) guidelines recommend that gene carriers should limit their physical activities to those that are non-competitive and recreational, the current ACCF/AHA guidelines do not recommend against the participation of gene carriers in competitive sports, particularly if there is no family history of HCM-related SCD. Yet, it is noteworthy that documented exercise-induced, sustained, ventricular arrhythmias are rare and most patients suffer an SCD and/or receive an appropriate shock during sedentary activities. Hypertrophic cardiomyopathy has been shown to be one of the leading causes of SCD in athletes younger than 40 years old. Interestingly, a recent meta-analysis has found that in young (ages ≤35 years) athlete subjects, there was no significant difference in HCM vs. structurally normal hearts after SCD. It is noteworthy that SCD is a very rare event in young athletes with an incidence in most studies of 1:8000–1:20000. Furthermore, recent studies from France and Denmark have shown that SCD is extremely uncommon among competitive athletes and is even less frequent than in either recreational sports participants or the general population. Nonetheless, some countries such as Italy have implemented pre-participation screening of competitive athletes by history taking, physical examination, and electrocardiogram. Early studies from the Veneto region in Italy showed an 89% decrease in the incidence of SCD in young competitive athletes during a 26 years screening period. However, a later study comparing the incidence of SCD among young athletes in Veneto and Minnesota, USA, has failed to show a lower mortality rate associated with pre-participation screening programmes. Hence, the need for pre-participation screening is still debatable.

### Current guidelines for implantable cardioverter defibrillator therapy
Until recently, the ACC and ESC shared a consensus document with joint recommendations for ICD implantation in HCM. However, in recent years major differences have evolved between the North American and European approaches to risk stratification and indications for ICD implantation.

In 2003, the ACC and the ESC established joint guidelines for SCD risk stratification and ICD implantation, based on assessment of the presence or absence of five conventional risk factors. Previous studies found that the risk for SCD correlated with the number of risk factors. Thus, the presence of two or more risk factors in an individual patient was considered an indication for ICD therapy for primary prevention, whereas the recommendation for ICD implantation in patients with only one risk factor was less clear. The recent (2011) ACCF and AHA guidelines have the same recommendation as the previous guidelines for patients with multiple risk factors; however, in contrast to the 2003 ACC/ESC guidelines, the current guidelines recommend ICD implantation (class IIa indication) for patients with severe hypertrophy, family history of SCD or recent unexplained syncope alone. This is based on an international registry of 506 patients, which showed that among patients who were selected for ICD implantation based on clinical risk features, the number of risk factors did not correlate with the rate of subsequent appropriate device discharge. The guidelines consider the other two conventional risk factors: NSVT (especially in patients younger <30 years) and abnormal blood pressure response to exercise sufficient justification for ICD implantation only in the presence of other SCD risk factors or modifiers, such as extensive LGE. The role of extensive LGE as a determinant factor in these borderline cases is one of the most important discrepancies between the ACCF/AHA and the ESC guidelines.

The recent ESC guidelines on HCM endorsed a novel clinical risk prediction model, which gives a prognostic score and is accessible as an interactive online calculator. The model was derived from a
retrospective, European multicentre longitudinal cohort study of 3675 patients with HCM and provides an individualized risk score. Eight clinical variables, which had been independently correlated with SCD in one or more studies, were included as pre-specified predictors. Of these, seven were associated with SCD at the 15% significance level and thus have been included in the final formula. Each of the predictors has a specific relative ‘effect’. Four of the parameters are major conventional risk factors (family history of SCD, maximal wall thickness, NSVT, and unexplained syncope), whereas three are novel risk factors including left atrial diameter, LVOT gradient at rest/Valsalva manoeuvre, and age at evaluation.

Table 1 summarizes the differences between the ESC and the ACCF/AHA guidelines. Unlike the ACCF/AHA guidelines, the calculator gives each risk factor a ‘relative weight’ and adjusts the risk for the same risk factors according to the patient’s age. Additionally, in contrast to the ACCF/AHA guidelines, it treats the continuous variables as such instead of determining an ‘artificial cut-off’ and turning them into binary variables. Surprisingly, there was an inverted U shape relationship between maximal wall thickness and the risk for SCD, where the risk tended to decrease in patients with extreme hypertrophy (≥ 35 mm). This is accounted for in the risk prediction model by the inclusion of a quadratic term for maximum LV wall thickness. The low number of such patients included in the analysis might explain this finding. Hence, the authors note that the calculator should be used cautiously in patients with a maximal wall thickness ≥ 35 mm. The calculator, on the other hand, does not incorporate newer risk factor modifiers, such as LGE on CMR, whereas it incorporates left atrial diameter, which is not the recommended method for measuring left atrial dilatation as it has many pitfalls. The model incorporates LVOT gradient assessed at rest and with the Valsalva manoeuvre. Notably, it has been shown that the Valsalva manoeuvre has a lower sensitivity (40%) than exercise echocardiography for the detection of latent obstruction and may underestimate the magnitude of provokable LVOT gradient. As such, the calculator does not truly incorporate maximal latent obstruction. Furthermore, LVOTO is a modifiable risk factor and indeed a number of studies have shown reduced risk for SCD and appropriate ICD discharge post-septal reduction treatment. Yet, the model is not validated for use in patients who have undergone myectomy or alcohol septal ablation. In addition, LVOT gradient is dynamic, and often changes spontaneously, albeit the calculator does not specify which gradient to use: most recent gradient with/without medical treatment versus maximal gradient pre-treatment. It is worth mentioning that the median LVOT gradient among the cohort of patients was relatively low (11 and 18 mmHg among patients without and with SCD, respectively). Notably, persons older than 65 years of age were scarcely represented in the cohort.

The variables are entered into a formula and an online calculator produces a 5-year risk for SCD on which the patients are stratified.

### Table 1  The differences between the European Society of Cardiology and the American College of Cardiology Foundation/American Heart Association guidelines recommendations for risk stratification for sudden cardiac death in hypertrophic cardiomyopathy

<table>
<thead>
<tr>
<th>Variable</th>
<th>ESC guidelines</th>
<th>ACCF/AHA guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong> (years)</td>
<td>Age at evaluation</td>
<td>Not incorporated into the risk stratification algorithm</td>
</tr>
<tr>
<td>Maximum LV wall thickness (mm)</td>
<td>Used as a continuous variable. In the HCM risk-SCD, there was a non-linear</td>
<td>Used as a binary variable where LV wall thickness &gt; 30</td>
</tr>
<tr>
<td></td>
<td>relationship between the risk of SCD and maximum LV wall thickness. This is</td>
<td>mm considered a major risk factor for SCD</td>
</tr>
<tr>
<td>LVOT gradient (mmHg)</td>
<td>The maximum gradient measured at rest or on Valsava, irrespective of</td>
<td>Not incorporated into the risk stratification algorithm</td>
</tr>
<tr>
<td></td>
<td>concurrent medical therapy</td>
<td></td>
</tr>
<tr>
<td>LA size (mm)</td>
<td>LA diameter determined by 2D echocardiography or M-mode</td>
<td>Not incorporated into the risk stratification algorithm</td>
</tr>
<tr>
<td>NSVT</td>
<td>Binary variable (yes = 1, no = 0)</td>
<td>Minor risk factor, which constitutes an indication for an</td>
</tr>
<tr>
<td>Family history of SCD</td>
<td>Binary variable (yes = 1, no = 0)</td>
<td>ICD in the presence of other SCD risk modifier</td>
</tr>
<tr>
<td>Unexplained syncope</td>
<td>Binary variable (yes = 1, no = 0), history of syncope irrespective of the</td>
<td>Major risk factor, which constitutes an indication for</td>
</tr>
<tr>
<td>Blood pressure response to</td>
<td>Not incorporated in the risk prediction model</td>
<td>ICD as a sole risk factor</td>
</tr>
<tr>
<td>exercise</td>
<td></td>
<td>Recent unexplained syncope is a major risk factor, which</td>
</tr>
<tr>
<td>Risk modifiers (LGE on CMR, large-sized LV apical aneurysm)</td>
<td>Not incorporated in the risk prediction model</td>
<td>constitutes an indication for an ICD as a sole risk factor</td>
</tr>
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into three groups for ICD recommendation: >6%/5 years (ICD should be considered), <4%/5 years (ICD generally not indicated), and 4–6%/5 years (ICD may be considered).

The ESC HCM outcome investigators conducted a validation study on 3066 HCM patients with a complete data-set. Using a threshold of ≥4% SCD risk in 5 years the number of patients needed to treat (NNT) with ICD therapy to postpone one SCD in 5 years was 16. Notably, this is comparable with the absolute reduction (6.9%) in mortality (NNT 14) with ICD as primary prevention in heart failure observed in the SCD in Heart Failure Trial. An external validation study on 706 HCM patients from two tertiary centres in Belgium and the Netherlands found the risk score to be a better discriminator between high- and low-risk patients than the recent ACCF/AHA and the 2003 guidelines. The mean calculated 5-year SCD risk in patients reaching the SCD endpoint was 4.9% with an NNT similar to the original study of 17 when compared with 22 and 20 according the 2003 and 2011 guidelines, respectively. In contrast, a retrospective validation study on 1629 patients demonstrated that although the risk score had high specificity it lacked sensitivity, where most patients with SCD or appropriate ICD interventions were misclassified by the risk score as low risk. Furthermore, >90% of the patients without an event and with a low-risk score had already been judged to be at low risk according to the conventional risk factors.

In summary, the calculator is accessible and enables clinicians to demonstrate to the patients their risk of SCD in a tangible manner and facilitate shared and personalized discussion with the patients.

Assessing the risk for SCD of the individual patient may be straightforward when both guidelines agree. However, in a considerable subset of patients the guidelines disagree regarding the need for prophylactic ICD implantation and the clinician is left with no choice but to follow one or the other. There are advantages but also limitations in using either guideline alone. Regardless of which guidelines are used our ability to correctly predict SCD risk remains imperfect and sometimes humbling.

Figures 2 and 3 illustrate cases from our centre where both guidelines did not recommend an ICD implantation, yet the first patient received an ICD followed by an appropriate shock and the second died an SCD. Notably, the ESC risk calculator is not applicable to the paediatric population (<16 years of age). However, the ESC guidelines recommend that Implantation of an ICD should be considered in children who have ≥2 major risk factors used in the adult population. The ACCF/AHA state that an ICD is reasonable for high-risk children with HCM, based on unexplained syncope, massive LV hypertrophy, or family history of SCD.

**Implantable cardioverter defibrillator-related factors influencing decision making**

Implantable cardioverter defibrillators have been proved to be highly effective in terminating life-threatening ventricular arrhythmias in patients with various cardiac diseases. Nevertheless, concerns were initially raised regarding the effectiveness of ICDs in HCM due to theoretical problems with cardioversion of hypertrophied hearts. Fortunately, these concerns were demonstrated to be unfounded. In the largest series of HCM patients with ICDs, 103 patients received ≥1 appropriate therapies. All but 1 were immediately successful in restoring sinus rhythm. The single patient who died suddenly was subsequently found to have had a rare device malfunction. These results were supported by several other studies demonstrating very rare cases of sudden death despite ICD implantation.

The main limitation prohibiting a more wide-spread use of ICDs in patients with HCM is the high rate of device-related complications. In the largest series of HCM patients with ICDs, during a mean follow-up period of 3.7 years 27% suffered complications, including inappropriate therapies. In a recent meta-analysis including 2190 patients, the annual appropriate and inappropriate intervention rate was 3.3 and 4.8%, respectively. The annual device-related complication rate (lead dislodgment/malfunction, infection, or significant psychological ramifications) was 3.4%. Although the devastating effects of SCD cannot be compared with such complications their impact on quality of life should not be underestimated. As in non-HCM patients, risk factors associated with inappropriate therapies include younger age and atrial fibrillation.

Device-related complications are of a specific concern in young patients because of their longer life expectancy. This translates into more pulse generator changes and a higher risk of lead failure and other complications. The recently developed subcutaneous ICD (S-ICD) offers an attractive alternative, as it is entirely extra-cardiac. Yet two major issues limit its current use in HCM: (i) most arrhythmic events in HCM patients are monomorphic VTs which are potentially treatable with anti-tachycardia pacing (ATP). Subcutaneous ICD therapeutic options, however, do not include ATP and are limited to high-voltage (and painful) shocks. (ii) QRS-T morphology screening is required prior to S-ICD implantation in order to ensure accurate sensing by the subcutaneous electrodes. Baseline QRS-T abnormalities frequently seen in patients with HCM may increase the failure rate of such screening, although this has not been demonstrated by all studies. Thus, the S-ICD is currently a good alternative for patients who have a contraindication for a transvenous pacemaker and who do not require concomitant pacing. In other cases, a transvenous ICD is usually implanted but an S-ICD may be considered after careful consideration of its advantages and disadvantages.

**Real-world decision making data from hypertrophic cardiomyopathy experts**

In order to learn more on the actual implementation of the guidelines by HCM experts especially in cases where decision making is inconsistent and determine differences in practice by geography, we conducted a survey among HCM experts practicing in recognized HCM centres of excellence with high volume of patients in different geographical areas.

The cases are summarized in Table 2. The responses and the ESC and ACCF/AHA recommendation for each case are shown in Table 3.

Case 1 demonstrates that, as expected by the differences in regional guidelines recommendations, most HCM experts (10/13) practicing in the USA and only one (1/8) of those practicing in Europe would recommend an ICD for primary prevention when...
maximal wall thickness $\geq$ 30 mm is the sole high-risk feature. These differences between the guidelines also exist for family history of SCD or unexplained syncope as the sole risk factor. Two review papers (point/counterpoint) were recently published each supporting the opposing opinions expressed in the ACCF/AHA and the ESC guidelines regarding an isolated risk factor of family history of SCD as a primary indication for an ICD implantation in HCM.  

Case 2 shows that although an ICD is not recommended by the ESC risk calculator, $>50\%$ (5/8) of HCM experts in Europe participating in the survey would recommend an ICD. This is most likely as

Figure 2 Cardiac magnetic resonance images of a 25-year-old man who had no conventional risk factors for sudden cardiac death but underwent an implantable cardioverter defibrillator implantation for primary prevention given maximal wall thickness of 28 mm and extensive late gadolinium enhancement. A month following the implantation he had symptomatic VT/VF requiring a defibrillatory shock. His estimated 5-year risk for sudden cardiac death according to the European Society of Cardiology calculator was only 2.2% and there was no compelling risk factor to warrant an implantable cardioverter defibrillator implantation according to the American guidelines. Nevertheless, the combination of severe hypertrophy of almost 30 mm along with extensive scar burden led to the decision to implant an implantable cardioverter defibrillator. (A) Apical four-chamber view (B). Short-axis view at mid ventricle. (C) Extensive late gadolinium enhancement at the mid ventricle.

Figure 3 An asymptomatic 14-year-old female with a maximal wall thickness of up to 21 mm on 2D echocardiogram (A) and cardiac magnetic resonance imaging (B), respectively. Genetic testing revealed a Troponin T mutation. She died a short time after being diagnosed with hypertrophic cardiomyopathy despite having no risk factors according to both the European Society of Cardiology and American College of Cardiology Foundation/American Heart Association guidelines (negative family history, normal BP response to exercise, no history of syncope, normal Holter monitoring, and no late gadolinium enhancement on magnetic resonance imaging).
the patient has two major risk factors including severe hypertrophy and family history of SCD.

Case 3 illustrates that although the ESC risk calculator does not incorporate LGE and apical aneurysm and thus does not recommend an ICD in this scenario, 50% (4/8) of experts practicing in Europe would recommend an ICD. Specifically, three of the eight HCM experts from Europe, who would not recommend an ICD when the only risk factor is severe hypertrophy, would now recommend an ICD given the presence of severe LGE and apical aneurysm. Thus, it can be seen that although scar burden and apical aneurysm are not taken into consideration in the ESC risk calculator some physicians practicing in Europe do consider them as risk factors.

Case 4 shows that nearly one-third (4/13) of HCM experts practicing in the USA would not follow guidelines recommendation for an ICD, as the patient is 60 years old. This is likely based on a recent study by Maron et al. showing low risk of SCD among HCM patients of 60 years of age or older even with conventional risk factors for SCD. In contrast, 50% (4/8) of experts practicing in Europe would recommend an ICD even though this is not in line with the ESC recommendations.

In Case 5, there was a consensus among experts worldwide that an ICD would not be warranted. Specifically, none of the experts practicing in Europe would follow the ESC recommendations for an ICD. This is most likely as the patient has none of the conventional risk factors and his increased estimated risk is driven by a high LVOT gradient and dilated LA alone.

In Case 6, similar to the previous case, only one of eight experts practicing in Europe would follow the ESC recommendation and recommend an ICD. This is most likely given the fact that the high calculated risk is driven by NSVT and dilated LA. Interestingly, though the ACCF/AHA recommendation for ICD when NSVT is the sole risk factor is only class IIb (especially in patients younger than 30) 2 of 13 experts from the USA would recommend an ICD in a 45-year-old person whose only risk factor is an NSVT.

Cases 5 and 6 highlight that although LA dilatation has been shown in two studies to be independently related to SCD in...
HCM and has been thus incorporated into the ESC calculator, most physicians do not appear to give it independent weight clinically when making a decision on ICD implantation.

In Case 7, only 50% (4/8) of experts from Europe and 60% (8/13) of experts from the USA would follow the ESC and ACCF/AHA recommendations, respectively.

Interestingly, nearly 40% of experts from the USA would recommend an ICD for a maximal wall thickness of 27 mm in combination with NSVT. This demonstrates that although the ACCF/AHA guidelines treat the maximal wall thickness as a binary parameter with a cut-off of 30 mm, a substantial number of experts practicing in the USA consider severe hypertrophy a risk factor even when the maximal wall thickness has not reached the cut-off of 30 mm.

As per the guidelines recommendation, all experts but one recommended an ICD implantation in Cases 8 and 9. However, it is noteworthy that indeed, the guidelines agree in these cases, however, for different reasons. These cases illustrate the fact that the European risk calculator takes younger age into account and treats the maximal wall thickness as a continuous variable, while the ACCF/AHA guidelines consider severe LGE and apical aneurysm as important risk factors.

**Summary**

Although the risk of SCD in HCM is low, great efforts should be made to identify the small subset of patients who will experience SCD. Unfortunately, a large number of SCDs occur in patients who are apparently at low risk, making it difficult to develop a method of precisely identifying these patients. It is extremely difficult to predict a clinical event such as SCD as it is determined not only by genetics but also by environmental factors such as myocardial ischaemia. The two sides of the Atlantic give inconsistent and at times conflicting recommendations for ICD implantation for primary prevention in HCM and are based on incomplete data. The clinician’s greatest challenge is to manage those patients who are judged to have neither high- nor low-risk profile for SCD.

A great deal can be learned from the survey on the real-world practice of HCM experts around the globe. The survey demonstrates that neither experts in Europe nor those in the USA follow their guidelines in a consistent manner, especially when no consensus exists between the different guidelines. In these cases, the decision regarding ICD is most probably based on personal clinical experience. There are five major differences between the guidelines, which we need to resolve in order to bridge the gap. These include incorporation of LVOT gradient, LA diameter and age as significant risk factors into the ESC calculator and the different usage of the maximal wall thickness by the two guidelines (continuous vs. binary variable). Finally, the greatest disagreement between the guidelines is about the importance of quantitative scar burden assessment by LGE as well as apical aneurysm. According to our survey, it appears that LVOT gradient and LA diameter are used in clinical decision making by experts from Europe to a lesser extent than suggested. Additionally, a substantial number of experts practicing in Europe consider severe LGE and apical aneurysm as significant risk factors for SCD. At the same time, our survey shows that the maximal wall thickness is treated as a continuous variable rather than binary by a significant number of experts from the USA.

**Collaborative studies**, specifically addressing these issues, are required in order to generate agreement. These should, however, assess whether LA volume index is a risk factor for SCD rather than LA diameter, as this is often an inaccurate measure of true LA size.

Unfortunately, there is still a subset of patients with no known high-risk factors who experience an SCD. This reflects limitations in what we know about HCM and that the different risk stratification algorithms are far from perfect. Hypertrophic cardiomyopathy dedicated centres worldwide should collaborate and conduct an international prospective cohort study which may shed light on the predictors for SCD in HCM and enable better evidence-based decision.

**Authors’ contributions**

A.W.-S., A.A., L.W., C.G., H.R. conceived and designed the research. A.W.-S., A.A., L.W., C.G., H.R. drafted the manuscript. A.W.-S., A.A., L.W., C.G., H.R. made critical revision of the manuscript for key intellectual content.

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