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How to assess sudden cardiac death risk in hypertrophic cardiomyopathy? Current challenges and directions for the future

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ABSTRACT

Over the past decade, knowledge about the risk of sudden cardiac death (SCD) in patients with hypertrophic cardiomyopathy (HCM) has advanced significantly. A standard well-recognised approach to risk stratification is based on the fundamental risk factors and SCD risk models that should be incorporated into the shared decision-making process. More detailed analysis including additional indicators, such as reduced left ventricular systolic function, the presence of late gadolinium enhancement or in some cases genetic variants, may provide valuable insights for intermediate-risk patients, enabling more personalized diagnosis and treatment. Risk stratification remains challenging in specific groups, such as patients who have undergone septal reduction therapy, those taking mavacamten, or those with phenocopies of HCM. The advancement of modern methodologies, including multifactorial approaches supported by

artificial intelligence algorithms, offers hope for more precise and individualized SCD risk assessment in individuals with HCM.

Key words: artificial intelligence, hypertrophic cardiomyopathy, prediction, risk, sudden cardiac death

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is an autosomal dominant genetic heart disease characterized by left ventricular (LV) hypertrophy and myocardial fibre disarray [1]. Epidemiological studies suggest that the incidence of HCM in the general population is between 1 in 200 and 1 in 500 people, with a male predominance [2]. HCM is diverse regarding age of onset, clinical phenotype, and natural history. The diagnosis and management of cardiomyopathies are subject to regional variations but there are only single studies that has systematically evaluated the clinical pathways of patients with HCM [3, 4]. Sudden cardiac death (SCD) is recognised to be an important cause of mortality with a reported annual incidence of 0.5-0.8% in adults and 1.2%–1.5% per year in children [5, 6]. Implantable cardiac defibrillators (ICD) are effective at treating malignant ventricular arrhythmias in individuals with HCM [7, 8]. The limited availability of certain diagnostic tests and the diversity of HCM phenotypes can hinder accurate risk stratification for SCD and the appropriate selection of therapeutic strategies .Identification of patients at the highest risk of arrhythmic events is therefore an important part of clinical care. Secondary prevention ICDs are indicated for HCM patients who have experienced a prior malignant ventricular arrhythmia (resuscitated out of hospital arrest or sustained ventricular tachycardia) but identifying who may benefit from a primary prevention device is more challenging. Our understanding of the risk factors for SCD has developed over time leading to the development of risk prediction algorithms that provide an individualized estimate of SCD risk and whose use is recommended for primary prevention ICD implantation decision-making [9, 10].

MECHANISMS OF ARRHYTHMOGENESIS IN HCM

The etiology of cardiac arrhythmias in HCM is complex and multifactorial. Proposed pathophysiological mechanisms include conduction dispersion associated with myocyte hypertrophy and disorganization, abnormalities related to intracellular calcium flux, conduction slowing in and around areas of fibrosis, and abnormal activity of distal Purkinje fibres [7, 9].

Sudden cardiac death in patients with HCM is most often caused by VT and VF [10]. However, due to limited ventricular filling and outflow obstruction and reduced cardiac output, even slower ventricular tachyarrhythmias may be poorly tolerated by patients with HCM, leading to syncope or SCD. Based on analysis of ICD electrograms in patients with HCM, the most common type of ventricular tachyarrhythmia was VF (50% of all episodes), followed by monomorphic VT (38%) and ventricular flutter (12%) [13] (Figure 1). Episodes of VF/ventricular flutter can be associated with exercise, highlighting the potential role of ischemia and abnormal/triggered automaticity as factors contributing to arrhythmogenesis [14, 15].

RISK STRATIFICATION FOR PRIMARY PREVENTION OF SCD — THE EVOLUTION OF RISK PREDICTION APPROACHES

Methods for assessing the risk of SCD and the indication for ICD implantation as part of primary prevention have evolved over the last two decades. It is widely accepted that certain demographic, clinical, and imaging characteristics are important indicators of the risk of SCD associated with HCM.

Historical observational population studies identified certain clinical risk factors associated with an increased risk of sudden death, which included VF or spontaneous VT, unexplained syncope, family history of SCD, max LVWT ≥30 mm, abnormal blood pressure response, non-sustained ventricular tachycardia (nsVT). In 2003, these were incorporated in the first risk stratification guidelines for HCM in a joint consensus statement by the American College of Cardiology Foundation (ACC)/American Heart Association (AHA) and European Society of Cardiology (ESC) which recommended considering an ICD in the presence of one or more clinical risk factors [11]. Although the assessment of these clinical risk factors continues to be important for the risk stratification of patients, this approach, which provides relative rather than absolute estimates of risk, has been shown to have limited power to distinguish high and low-risk patients. To address these concerns, in 2014 the first risk prediction algorithm (HCM Risk SCD) was developed using a large European cohort of adult (>16 years) patients with HCM. This model uses 5 routinely available clinical risk factors (patient's age, maximum LV wall thickness, left atrium size, LV outflow tract (LVOT) gradient, family history of SCD, presence of nsVT, and unexplained syncope) to calculate an individualised estimate of 5-year SCD risk [16]. Some studies have raised concerns that this approach may have a lower sensitivity to identify patients at risk of events [10] but multiple independent external validation studies have confirmed that this risk model provides accurate

risk estimates that be used as part of a shared decision-making process to guide ICD implantation [17].

Historically there has been a divergent approach to risk stratification in North America and Europe with risk calculators adopted by the ESC guidelines in 2014 and ESC/AHA guidelines continuing to recommend a single risk factor approach to risk stratification [18]. However, the most recent ESC and AHA/ACC guidelines published in 2023 [19, 20] and 2024 [19, 21] respectively both now recommend the use of risk calculators as part of risk stratification decision-making. Some differences remain concerning the treatment of additional risk factors and when risk calculators should be used (for all patients in ESC guidelines and only when 1 or more risk factors are present in AHA/ACC guidelines). Generally, the highest-risk patients are identified by both risk stratification approaches, but the single risk factor approach leads to more ICDs implanted in lower-risk patients who will potentially be exposed to device-related complications including inappropriate therapies [21–25]. This is why, there is an agreement from both guidelines that individualised estimates of risk are a helpful tool for use as part of a shared decision-making process.

The use of some other potential risk factors, not currently incorporated in SCD risk calculators that may be helpful in decision making has been the subject of recent interest. Studies have described a higher risk of sudden death events in patients with LV systolic dysfunction (LV ejection fraction [LVEF] <50%). However, the additional value of systolic dysfunction on top of risk calculator estimates is unclear. Guidelines differ in the approach to patients with systolic dysfunction. The AHA/ACC recommend that it is considered a major risk factor meaning ICD implantation is reasonable [21], whereas the ESC recommend estimating SCD risk using risk calculators and then incorporating the presence of dysfunction in shared decision-making [20].

The presence of fibrosis as assessed using late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) is associated with SCD risk and it has been suggested that adding this variable to the risk calculator may improve the stratification of low or intermediate-risk patients. There remain practical concerns about the methods used to quantify LGE and some uncertainties exist about how best to incorporate LGE in risk stratification decisions, which is reflected in the guidelines.

Finally, LV aneurysms have been included as a major independent SCD risk factor in the most recent AHA/ACC guidelines meaning they are considered a reasonable sole indication for ICD implantation [21]. In contrast, they are not considered risk factors in the current ESC guidelines [20]. The reason for this is that studies reporting an association have all been small

retrospective studies, apical aneurysms are relatively common (up to 5% of individuals), most patients who developed ventricular arrhythmias also had other “conventional” risk factors, and most ventricular arrhythmias were monomorphic ventricular tachycardia rather than VF, meaning the predictive value of apical aneurysms is difficult to assess [20–22].

Possible associations of other clinical risk factors with sudden death have also been described, including B-type natriuretic peptide levels, atrial fibrillation, and the New York Heart Association functional class. However, the evidence supporting their use in risk stratification decision-making is limited (Table 1).

A summary of the risk factor significance in the consecutive European and American guidelines is presented in Table 1 and Table 2.

While discussing the indication for ICD implantation for primary prevention of SCD, we should be aware of the differences in race-related risk factors, especially between European and American HCM populations. On the other hand, it is also important to recognise the impact that differences in HCM care and healthcare systems have on ICD implantation decision-making.

SCD RISK STRATIFICATION IN SPECIAL CASES

SCD risk stratification and therapy

Mavacamten

Of note, there is increasing interest in the effect of myosin inhibitors (e.g., mavacamten) on arrhythmic risk in HCM. Theoretically, it may reduce the potential for malignant ventricular arrhythmias by alleviating LVOT obstruction and lowering ventricular filling pressures. However, a small subset of patients receiving myosin inhibitors may develop transient LV systolic dysfunction, potentially increasing the risk of arrhythmia. Current data come from studies with relatively small patient groups and randomized trials that are insufficiently powered to provide reliable information on SCD or similar events [15, 19, 23–27].

Mavacamten has been studied for its potential to reduce the need for septal reduction therapy (SRT) in patients with obstructive HCM. In EXPLORER-HCM trial, patients receiving mavacamten demonstrated significant improvements in symptoms, functional status, and outflow tract gradients compared to those on placebo. The study showed that after 16 weeks of treatment, the proportion of patients meeting guideline criteria for SRT was significantly lower in the mavacamten group (17.9%) compared to the placebo group (76.8%) [26].

Currently mavacampten is dedicated only for well-characterized group of symptomatic patients with obstructive HCM. Moreover, the therapy needs individualization [26]. Both genetic testing before drug implementation and regular LVEF and LVOT gradient assessment

is required for careful dose titration to achieve an appropriate target LVOT gradient while maintaining LVEF ≥50% and avoiding heart failure symptoms. All these make the SCD risk assessment in patients receiving mavacamten even more difficult.

From the practical point of view, LVOT gradient is a component of SCD-Risk score thus the use of SCD-Risk calculator should be validated in this new population of HCM patients.

The long-term outcomes of myosin inhibitors therapy, including potential arrhythmic risks, remain to be determined.

Septal reduction therapy

There is a lack of evidence about the best way to assess the risk of SCD in patients who have undergone SRT. Indeed, the HCM Risk SCD calculator uses maximal LVOT gradient as a clinical predictor but is not validated in this patient group. Previous studies have suggested that the risk of arrhythmia is reduced after surgical myectomy [23–25]. This may be due to improved hemodynamics, which reduces unfavourable conditions favouring arrhythmias, such as increased ventricular filling pressure or subendocardial ischemia. There are greater doubts about the beneficial antiarrhythmic effect in cases of alcohol ablation due to the smaller reduction in septal mass [15].

Data from the international SHaRe (Sarcomeric Human Cardiomyopathy Registry) shows that event-free survival of HCM patients after SRT at 10 years was 83% and ventricular arrhythmias were rare. After 6.8 years from SRT, 4% experienced HCM-related death (0.6% per year), 13% a composite HF outcome (1.9% per year), and 5% a composite ventricular arrhythmia outcome (0.7% per year). Among adults, older age at SRT was associated with a higher incidence of HCM death [28].

Both the AHA/ACC [21] and ESC guidelines [20] suggest caution in using standard methods for assessing SCD risk in patients after SRT [28].

Older patients with HCM

The age at which HCM is diagnosed is gradually increasing. According to the SHaRe registry, about a third of people diagnosed after 2010 were over 60 years old [15, 29]. Older patients usually have a milder form of HCM, with less LV ventricular hypertrophy and less phenotypic disease severity. This is associated with a less frequent occurrence of SCD risk factors. In a study conducted at two referral centres, patients diagnosed with HCM after the age of 60 had an annual disease-specific mortality of 0.64% and an annual SCD risk of 0.20% [22,30]. Similar results were observed in a multicentre European cohort, where the incidence of SCD or

equivalent events decreased with age. It is also worth noting that although nsVT and LGE are quite common in older HCM patients, their prognostic value as risk markers decreases with age [31, 32]. The HCM Risk-SCD calculator incorporates age in the risk estimates generated but it may be that current risk stratification strategies are more applicable to younger, middle-aged patients.

Children with HCM

The natural history and outcomes of HCM in childhood are highly variable and depend at least partly on the etiology and age of onset. Although the etiology is recognized to be more heterogeneous than adult populations, the majority of the disease is caused by sarcomeric protein variants. Patients with syndromic diseases (inborn errors of metabolism or RASopathy syndromes) or with early onset (in the first year of life) have a worse prognosis [33, 34]. Syndromic causes of HCM include conditions such as Pompe disease, Fabry disease, and Noonan syndrome, each of which presents with distinct pathophysiological features and prognostic implications [33–44]. Pompe disease and Fabry disease represent inborn errors of metabolism, while Noonan syndrome belongs to the group of RASopathies, which are disorders caused by mutations in genes of the RAS/MAPK pathway. These syndromes often manifest with multisystem involvement, compounding the complexity of HCM management [33–44]. Studies in small, selected groups of patients from tertiary referral centres reported a high incidence of SCD in childhood, up to 7% per year [35]. However, more contemporary data from larger, representative population-based studies have described a lower true rate of SCD estimated at 0.8% to 2% per year [8, 36]. Outside of infancy, SCD is the most common cause of death in pediatric HCM, and recent population-based studies indicate that arrhythmic events account for over 50% of adverse events within 10 years of diagnosis, with a cumulative incidence of 8.8%. Recent studies indicate that children with HCM are at greater risk of arrhythmic events than adults, as highlighted by the SHaRE database, where patients with pediatric-onset HCM were 36% more likely to experience an arrhythmic event than those diagnosed in adulthood [36].

For a long time, understanding of risk factors for SCD in childhood was limited and extrapolated from adult studies. However, there is now a good evidence base to support SCD risk stratification in childhood. Many of the risk factors in childhood disease are the same as in adult practice (e.g. LV hypertrophy, left atrial diameter, nsVT, unexplained syncope, previous malignant arrhythmia) but there are important differences as well. Family history of sudden death has been shown in multiple studies not to be strongly associated with risk [37]. The

previously discussed HCM Risk-SCD model is not validated for use in childhood disease but in 2019 the first childhood risk prediction model (HCM Risk-Kids) was developed in a cohort of over 1000 children with non-syndromic disease meaning individualised estimates of risk could be calculated for the first time in pediatric patients [36]. A second model, PRIMaCY, was later published, which appears to have a similar ability to identify high-risk patients but may over-estimate risk in some patient groups leading to higher ICD implantation rates [38-40]. Both ESC and AHA/ACC guidelines recommend the use of pediatric-specific risk tools in ICD implantation decision-making in line with adult practice. There is limited data to support the use of additional risk factors (e.g. LV aneurysm, LV systolic dysfunction) in childhood practice. LGE is less frequently seen in childhood patients but has been described to be associated with other risk factors for sudden death and the degree of hypertrophy [41, 42]. In agreement with adult practice, a recent study showed an independent association of LGE with SCD events and suggested that the discriminatory ability of the pediatric risk models is improved by adding it to the calculated risk estimates. It remains unclear how to incorporate this in individual patients' ICD risk assessments [43, 44].

SCD risk assessment in HCM phenocopies — unresolved problem

Whilst HCM phenocopies are relatively rare, it is crucial to distinguish these conditions as their management and prognosis varies significantly from that of HCM with sarcomere mutations. The debate on SCD risk assessment and ICD implantation in patients with HCM phenocopies, i.e. cardiac amyloidosis (CA) or Anderson–Fabry disease (AFD) is still ongoing.

Retrospective analyses of the results of ICD implantation in patients with CA are few and often contradictory [45]. A review of data on 720 patients who had an ICD implanted found that although a quarter of them received appropriate ICD therapy, only 22% of these patients survived long-term follow-up. In approximately 68% of patients, the ICD probably did not affect survival [45]. The results of these studies vary, which may be due to differences in patient numbers, methodology, and the diversity of CA etiologies. One of the main problems is the retrospective nature of most studies and the fact that they included patients with different types of amyloidosis, making it difficult to draw valid conclusions. AL amyloidosis, associated with a higher risk of mortality, was suggested as an independent predictor of poor prognosis. Unexplained syncope, which is a common symptom in CA patients, may result from many different causes, which further complicates the qualification process for ICD implantation. Additionally, a decline in LV systolic function is a late symptom of CA, suggesting the need to use more advanced echocardiographic parameters to assess cardiac function [45].

The ESC in its 2015 consensus statement does not recommend prophylactic ICD implantation in patients with CA [18] and the 2019 Heart Rhythm Society guidelines only consider this option in patients with nsVT and an expected survival of more than one year. However, this is a class IIb recommendation, indicating limited certainty about the benefits [41].

Implantation of ICD in AFD is currently recommended mainly for patients who have suffered cardiac arrest with VF or VT, and for those who experience spontaneous, sustained VT leading to syncope or hemodynamic disturbances [46, 47]. This means that ICDs are mainly used as secondary prevention after symptomatic arrhythmia episodes. However, there is still controversy regarding the qualification criteria for ICD implantation as part of primary prevention.

A retrospective study from the United Kingdom found that 44% of patients with an ICD received the device for primary prevention, based only on the presumed risk of malignant arrhythmias and sudden cardiac death. These criteria included, among others: severe LV hypertrophy, extensive cardiac fibrosis, electrocardiography (ECG) abnormalities, previous episodes of nsVT and a family history of SCD [48]. Especially LGE in CMR, which is a marker of fibrosis, correlates with the occurrence of malignant ventricular arrhythmias and the risk of SCD.

Men with AFD have a shorter life expectancy than women, and the risk of SCD is greater in older male patients [46].

In conclusion, ICD implantation in AFD is mainly recommended as secondary prevention, while ICD use in primary prevention requires further research and assessment of individual risk factors [46].

SCD RISK STRATIFICATION — PERSPECTIVE FOR THE FUTURE [2]

Genetics and risk stratification associated with HCM

Genotype-positive HCM has been described to have a worse prognosis with higher rates of disease-related complications [29, 47]. However, the role of genetics in risk stratification remains uncertain. Early studies suggested that particular genes were associated with an increased risk of sudden death, but subsequent studies have reported conflicting findings [41]. Recent research has identified specific high-risk mutations that may influence SCD risk. Variants such as MYBPC3 p.Val158Met, TNNT2 p.Lys263Arg, and MYH7 p.Val320Met have been associated with a more malignant phenotype and an elevated risk of sudden cardiac death [49]. Despite these findings, the use of genetic testing in routine risk stratification decision-

making remains limited. At present, genetic results are primarily utilized to guide family screening and identify carriers of pathogenic mutations [20, 21], while their role in direct clinical risk stratification for SCD requires further validation. We suspect that our “genetic fingerprint” may be a component of multiparameter individual risk analysis in the nearest future [49].

Modern imaging in the evaluation of “arrhythmogenic” burden

Novel CMR techniques — CMR native T1 mapping and extracellular volume fraction imaging used for quantitative myocardial tissue characteristics can predict SCD in HCM patients [50]; global native T1 mapping may improve risk stratification in HCM patients defined as a low SCD risk [51]. Global extracellular volume fraction was documented as being superior to LGE in the risk prediction (area under the curve 0.83 vs. 0.8) [52]. T2 mapping can also be an added value because it improves stratification in HCM subjects with LGE presence [52].

A detailed analysis of LV mechanics in echocardiography or CMR that can be recognized as a consequence of local LV remodelling and creates novel additional markers. Both LV strain reflecting myocardial inhomogeneity and LV apical fractal dimension corresponding to trabecular complexity have been demonstrated as predictors of SCD in HCM patients [45–56].

Modern arrhythmia monitoring/induction

Long-term ambulatory rhythm monitoring with implantable loop recorders may allow the timely detection of actionable high-risk arrhythmias that are often precursors of more malignant arrhythmias and SCD [57]. However, the cost-effectiveness and significance of short nsVT remain to be resolved.

Programmed electrical stimulation (PES) to stratify arrhythmic risk in HCM patients is still controversial due to its invasiveness and the fact that ventricular arrhythmias induced by PES are considered non-specific. PES is not considered in current guidelines [18].

However, according to the recently published data by Gatzoulis et al. [58], inducibility at PES predicts SCD or appropriate device therapy in HCM and non-inducibility is associated with prolonged event-free survival [58]. An analogous hypothesis was stated recently by Saumarez et al. [59]. Given an improved understanding of complex arrhythmogenesis, authors suggested that arrhythmic SCD is likely to be more accurately predictable using electrophysiologically based approaches and we should drive further development of electrophysiologically based methods [59].

Artificial intelligence

In the nearest future, artificial intelligence (AI) may play a key role in assessing the risk of SCD in patients with HCM. In current methods, based on clinical risk factors such as history of syncope and myocardial thickness, subtle differences between patients are often not taken into account. AI, especially machine learning algorithms, can revolutionize this assessment, enabling a more precise and personalized diagnosis.

In the coming years, AI may become an invaluable tool for analysing both ECG and heart images such as CMR and echocardiography. Thanks to advanced algorithms, AI will be able to identify even more accurately structural changes, such as fibrosis, which are strongly associated with SCD risk. Automatic segmentation using LGE images allows us to quantify automatically LV mass and fibrosis [60]. Recently it was documented that LV radionic features obtained from LGE images are an independent SCD risk factor in HCM (hazard ratio, 1.208–1.211) [61]. Radiomic analysis, a process of extracting a vast array of quantitative features from medical imaging, provides insight into the microstructural and functional heterogeneity of the myocardium that might not be visible to the human eye. By leveraging such data, AI can highlight patterns that correlate with adverse outcomes, such as arrhythmias or SCD. This opens up new avenues for stratifying patients based on imaging biomarkers and tailoring interventions accordingly, making AI-driven risk models increasingly reliable. Hopefully, integrating these data with genetic information will allow an assessment of how specific mutations affect a patient's risk.

The future will also bring new opportunities in heart rhythm monitoring and ECG analysis. AI algorithms will be able to detect subtle anomalies, i.e. induced by sympathetic dysregulation [62], that may signal the risk of ventricular arrhythmias and monitor patients in real time. Correlations with seasonal, and activity-related arrhythmia patterns may be of additional prognostic value. As a result, AI can provide automatic warnings of impending threats, enabling quick intervention and potentially saving lives.

However, despite its great potential, the future of AI implementation in SCD risk assessment requires further research and validation. It will also be crucial to maintain the role of doctors as decision-makers, who will use AI as a support and not as a replacement for their knowledge and experience. In the coming years, we can expect AI to become an integral part of cardiology, leading to more precise and personalized care for patients with HCM and other heart conditions.

SUMMARY

In summary, the field of risk stratification of SCD in HCM has advanced significantly over the past decade. Regardless of the fact that the standard, well-recognized risk factors have remained the same, the SCD risk models should be used as part of a shared-decision making process. Additional risk factors (e.g. impaired LV systolic function, LGE on CMR) may provide further valuable information for intermediate risk patients that allows for individualization and tailor-made treatment. Children with HCM are at higher risk of SCD but risk can be accurately assessed using pediatric specific risk tools. Ongoing real-world validation of the current risk stratification are still required Risk stratification remains challenging in some groups of patients — after septal reduction therapy, during mavacamten administration, in patients with HCM phenocopies. On the other hand, a novel approach based on multifactorial assessment supported by AI models will allow for individual risk scores hopefully in the near future (Figure 2) [54, 55].

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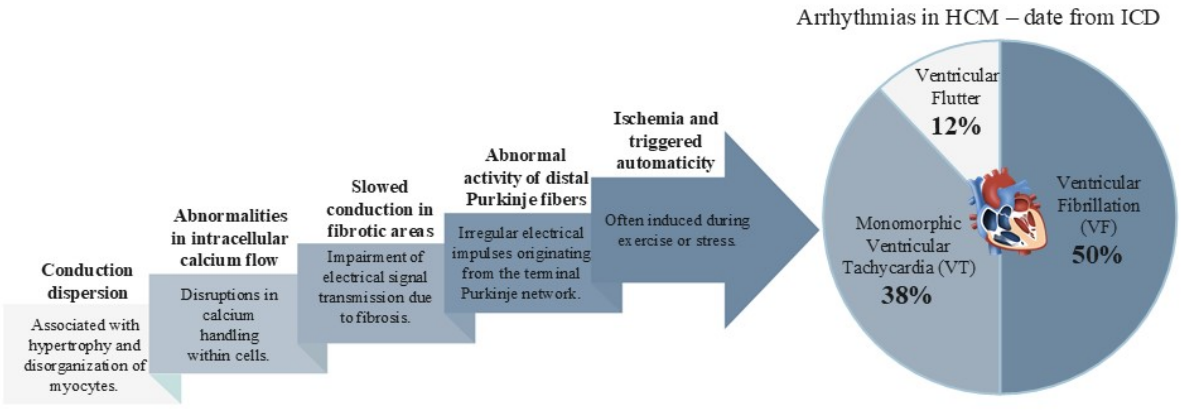

Figure 1. Arrhythmogenesis in hypertrophic cardiomyopathy (HCM) — mechanisms and types of ventricular arrhythmias

Abbreviations: ICD, implantable cardioverter-defibrillator

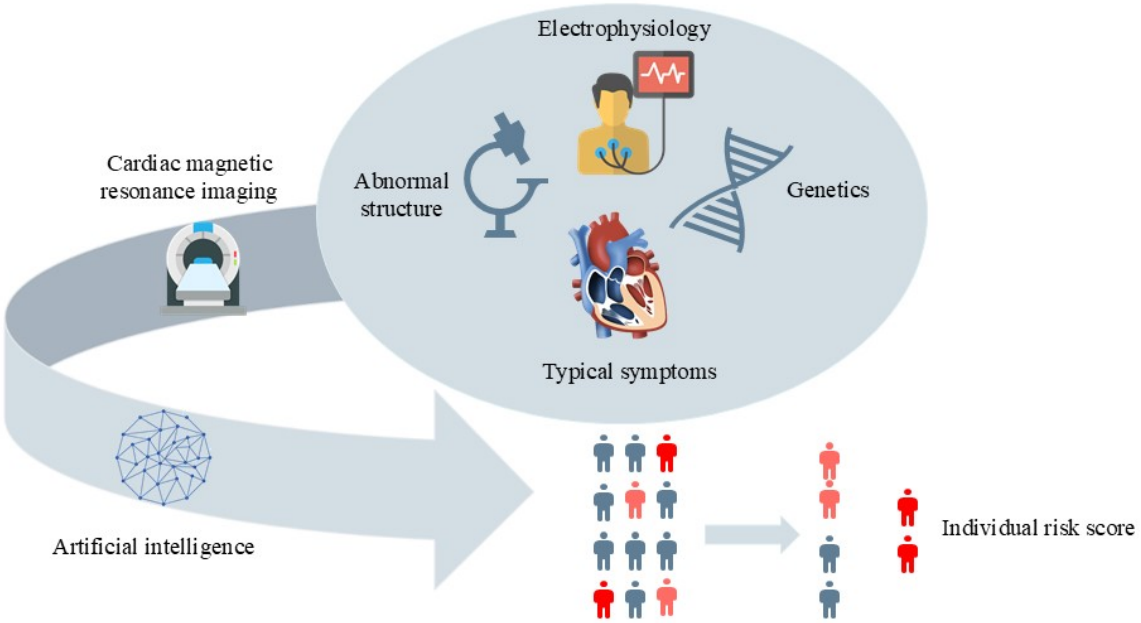

Figure 2. Potent novel approach for risk stratification of sudden cardiac death in patients with hypertrophic cardiomyopathy based on multifactorial assessment

Table 1. Risk factor of SCD in HCM

Risk factor	**ACC/ESC 2003 consensus**	**ACCF/AHA guidelines 2011**	**ESC 2014 guidelines**	**AHA/ACC/HRS 2017 guidelines**	**AHA/ACC 2019 enhanced strategy**	**AHA/ACC 2020 guidelines**	**ESC 2023 guidelines**	**AHA/ACC 2024 guidelines**
VF or spontaneous VT	+	–	–	–	–	–	–	–
Unexplained syncope	+	+	+	–	+	+	+	+
Unexplained syncope within 6 months	–	–	–	+	–	–	–	–
Family history of SCD	+	+	+	+	+	+	–	+
Family history of SCD at a young age (<40 years)	–	–	–	–	–	–	+	–

Max LVWT ≥30 mm	+	+	+	+	+	+	+	+ (in some cases ≥28 mm)
Abnormal blood pressure response	+	+	–	+	–	–	–	–
nsVT	+	+	+	+	+	+	+	+
Prior history of VF or sustained VT	–	+	–	–	–	–	–	–
Age	–	–	+	–	–	–	+	–
LV outflow tract gradient	–	–	+	–	–	–	+	–
LA diameter	–	–	+	–	–	–	+	–
Cardiac arrest (VT/VF)	–	–	–	+	–	–	–	–
Spontaneous sustained VT causing syncope or hemodynamic compromise	–	–	–	+	–	–	–	–
LV systolic dysfunction (LVEF <50% by echocardiography or CMR imaging)	–	–	–	+	+	+	+	+
Apical aneurysm	–	–	–	+	+	+	–	+
The extent of LGE ≥15% of LV mass	–	–	–	–	+	+	+	+
Genotype status	–	–	–	–	–	–	–	+

Abbreviations: ACC, American College of Cardiology; ACCF, American College of Cardiology Foundation; AHA, American Heart Association; ESC, European Society of Cardiology; HCM, hypertrophic cardiomyopathy; HRS, Heart Rhythm Society; LA, left atrial; LGE, late gadolinium enhanced; LV, left ventricle; LVEF, left ventricular ejection fraction; max; LVWT, maximum left ventricular wall thickness; nsVT, non-sustained ventricular tachycardia; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia

Table 2. Standard and novel risk factors for SCD in HCM — the role in the current ESC and ACC/AHA guidelines

Risk Factor	**Description/Cut points/**Role in current SCD risk assessment
Demographic and clinical characteristics	
Age	• The risk of SCD is highest in patients under 30 years of age and decreases as the patient ages. In patients over 60 years of age, the risk of SCD is less than 1%. In children relationship between the risk and age is nonlinear (the highest SCD risk at the age of 9–15 years). In the young HCM population, the significance of other risk factors (nsVT, LV hypertrophy, unexplained syncope) is of higher value. ESC guidelines — factor included in SCD Risk Score
Family history of sudden cardiac death (SCD)	A family history of SCD, defined as one or more deaths in first-degree relatives before the age of 40 years or sudden cardiac death at any age in a first-degree relative diagnosed with hypertrophic cardiomyopathy, increases the risk of SCD in a patient with HCM by up to 20%. In the HCM pediatric population, the SCD family history is of no significance. • ESC guidelines — factor included in SCD Risk Score • ACC/AHA guidelines — class IIa recommendation for ICD
Female gender	Women with hypertrophic cardiomyopathy (HCM) have higher all-cause mortality, probably due to heart failure, as there was no increased rate of arrhythmogenic deaths or ICD shocks
Genotype	The rate of SCD is higher in all groups of patients with HCM and a confirmed genetic mutation compared to patients without such a mutation. A meta-analysis of 7675 patients with HCM showed that the risk of SCD was 17% for mutations in the TNNT2 gene, 11% for mutations in MYH7, and 5% for mutations in MYBPC3. In HCM patients without a confirmed mutation, the risk of SCD was 0.4%. However, decisions about ICD implantation should not be based solely on the patient's genotype
Symptoms	
Unexplained syncope	Many studies have shown that unexplained syncope, defined as a single event of unknown cause in the last 6 months, is a marker of increased risk of SCD. HCM patients with a recent, unexplained loss of consciousness (less than 6 months ago) had a fivefold increased risk of SCD compared with patients without loss of consciousness. Older patients, defined as people aged 40 years and over, with recent episodes of loss of consciousness (more than 5 years before the first assessment) did not show an increased risk of SCD • ESC guidelines — factor included in SCD Risk Score • ACC/AHA guidelines — class IIa recommendation for ICD
Functional class according to the New York Heart Association (NYHA)	Patients with HCM in NYHA class III/IV have a higher risk of SCD compared to patients in class I/II
Structural abnormalities	

Maximum left ventricular wall thickness	Maximum left ventricular end-diastolic wall thickness, measured anywhere in the left ventricle and of at least 30 mm, is associated with an increased risk of SCD in patients with HCM • ESC guidelines — factor included in SCD Risk Score • ACC/AHA guidelines — class IIa recommendation for ICD
Left atrium (LA) dimensions	In clinical practice, it is assumed that the left atrial dimension assessed in M-mode or 2D echocardiography in the long-axis parasternal projection, exceeding 45 mm, may be considered a marker of increased risk of SCD in patients with HCM. • ESC guidelines — factor included in SCD Risk Score
Maximum gradient in the left ventricular outflow tract (LVOTO)	LVOTO is assessed at rest and during Valsalva manoeuvres using continuous and pulsed Doppler in 3-, 4- and 5-chamber projections. Most studies have shown a correlation between an LVOT gradient of ≥30 mm Hg and a worse prognosis in terms of SCD risk. • ESC guidelines — factor included in SCD Risk Score
Left ventricular (LV) systolic dysfunction	Left ventricular (LV) systolic dysfunction, defined as a left ventricular ejection fraction (LVEF) less than 50%, occurs in approximately 5–10% of patients with HCM and is associated with a worse prognosis, including an increased risk of SCD • ESC guidelines — used as an additional clinical risk factor • ACC/AHA guidelines — class IIa recommendation for ICD
Left ventricular apical aneurysm (LVAA)	Left ventricular apical aneurysm (LVAA) is rare among patients with HCM, occurring in less than 2% of patients, and is associated with a higher risk of arrhythmia and SCD. • ACC/AHA guidelines — class IIa recommendation for ICD
Late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR)	The presence of LGE on CMR examinations occurs in approximately 60% of patients with HCM and reflects the degree of myocardial fibrosis. Fibrosis is associated with an increased risk of ventricular arrhythmias and SCD. Each 10% increase in LGE is associated with a 40% increase in the relative risk of SCD. Extensive LGE is defined as ≥15% of LV mass • ESC guidelines — extensive LGE used as an additional clinical risk factor • ACC/AHA guidelines — extensive LGE — class IIb recommendation for ICD
History of arrhythmia – ECG, Holter monitoring	
Non-sustained ventricular tachycardia (nsVT)	Non-sustained ventricular tachycardia (nsVT), defined as at least 3 ventricular beats with a rate of at least 120/min lasting less than 30 seconds, occurs in approximately 20%–30% of patients with HCM over 40 years of age. One study suggested that the predictive value of nsVT was significant in HCM only in patients under 30 years of age, and the frequency, duration, and rate of nsVT were not significant. Another study showed that nsVT is associated with a higher risk of SCD in HCM only when it occurs repeatedly or is associated with symptoms. In summary, however, the

	predictive value of nsVT for SCD is not high, so nsVT alone is not sufficient to justify ICD implantation • ESC guidelines — factor included in SCD Risk Score • ACC/AHA guidelines — class IIa (children)/IIb (adults) recommendation for ICD
Atrial fibrillation	Atrial fibrillation occurs in approximately 20% of HCM patients and is associated with an increased risk of SCD and heart failure
Response to exercise	
Abnormal blood pressure response to exercise	An abnormal blood pressure response to exercise, defined as no increase in systolic blood pressure (SBP) of more than 20 mm Hg or a decrease in SBP of 10 mm Hg during exercise, occurs in more than one-third of patients with HCM and is an independent risk factor for SCD. Moreover, it is more visible in younger patients
ECG stress test	The occurrence of ventricular arrhythmias (VT/VF) during exercise is considered an important risk factor for SCD in HCM. Therefore, periodic exercise testing plays a key role in the risk assessment and monitoring of patients with HCM
Additional risk factors	
B-type natriuretic peptide (BNP) level	Although BNP is not included in the guidelines for indications for ICD implantation, as a cardiac biomarker it reflects the degree of heart failure. This may be important in assessing the risk of SCD in patients with HCM

Abbreviations: see Table 1