Arrhythmias and Sudden Death: What is New in Hypertrophic Cardiomyopathy?

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Abstract

Hypertrophic cardiomyopathy (HCM) is a complex genetic disorder that has garnered significant attention because of its diverse manifestations, including arrhythmias and heightened risk of sudden cardiac death. Advances in precision diagnostics, such as genetic testing and cardiac imaging with late gadolinium enhancement, have refined HCM diagnosis, enabling targeted therapeutic and risk stratification approaches. AF, prevalent in HCM, exacerbates symptoms and stroke risk, while ventricular arrhythmias pose a direct threat to survival. Catheter ablation offers symptom relief in AF patients with HCM, yet recurrence remains high because of unique myocardial changes, highlighting the need for refined patient selection and long-term monitoring. The risk of sudden cardiac death in HCM, particularly in younger individuals, underscores the importance of precise risk stratification tools such as the European Society of Cardiology HCM Risk-SCD model. The expanding role of ICDs and emerging pharmacological agents, including myosin inhibitors, marks a shift toward more individualised management of HCM. This review integrates recent developments in arrhythmia management, targeted therapies and risk assessment, offering a comprehensive perspective on HCM tailored to improve clinical outcomes through a precision-medicine lens.

Keywords

Hypertrophic cardiomyopathy, AF, heart failure, ventricular arrhythmia, sudden cardiac death, risk stratification, ICD

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Hypertrophic cardiomyopathy (HCM) is the most common hereditary cardiac disorder after familial hypercholesterolaemia, with a phenotypic incidence of one in every 500 individuals.[1] While some patients remain asymptomatic despite harbouring mutations in HCM genes, other patients have symptoms such as shortness of breath, palpitations, fatigue, leg swelling, chest pain and/or fainting. In some cases, structural and functional changes in the heart because of HCM can lead to supraventricular arrhythmias, such as AF, ventricular arrhythmias (VAs), heart failure or even sudden cardiac death (SCD).[2] While malignant arrhythmia and SCD are less often observed in HCM patients than in other hereditary cardiomyopathies, such as dilated cardiomyopathy or arrhythmogenic cardiomyopathy, the risk remains substantial. Advancements in genetic testing, screening and treatment options have dramatically changed the level of care HCM patients and their relatives receive, which is reflected in the most recent international guidelines.[3,4] Despite these successes, many areas of uncertainty and lack of evidence remain prevalent in the context of HCM, especially when arrhythmia is involved or suspected.

In this review, we aim to highlight current developments, trends and remaining challenges in detecting and treating AF and the prevention of SCD in patients with HCM.

AF and Hypertrophic Cardiomyopathy

AF remains the most common arrhythmia associated with HCM with a reported incidence of 20–25% in this population.[3] There is currently no organised screening effort besides yearly Holter monitoring included in the treatment and monitoring regimen for HCM patients. Thus, the true burden of AF in this population is likely to be higher than recent observational studies have suggested.[4]

The occurrence of AF is often accompanied by increased risk of stroke, development of heart failure and reduced quality of life.[5,6] Additionally, AF presents clinicians treating HCM patients with other challenges unique to this patient group since the typical structural and functional changes common in HCM can aggravate AF-related symptom burden and complicate treatment.[3,4] Comprehensive management, including anticoagulation, rate or rhythm control and addressing the underlying structural abnormalities of HCM, is essential to improving survival outcomes.

Genetics of AF and Hypertrophic Cardiomyopathy

Over time a number of genes have been identified as predisposing for the development of AF. Genes related to ion channels, structural proteins and signalling pathways are commonly implicated. Common and rare variants

in genes such as *KCNE2*, *KCNQ1* and *SCN5A*, which influence cardiac electrical activity, have been associated with increased risk of AF development.[7] Given the prominent role genetic testing has within the screening effort for HCM and other cardiomyopathies, it would be interesting to speculate on the possibility of extending the testing effort to genes predisposing to cardiac arrhythmias, such as AF, should the evidence confirm these suspected links.

Recent research has highlighted the potential of polygenic risk scores, which represent a quantifiable measure of an individual's genetic predisposition to certain diseases, calculated by aggregating risk variants identified through genome-wide association studies. Although specific mutations linked to AF have been studied, polygenic risk scores provide a broader genetic assessment by incorporating thousands of mainly common genetic variants with small individual effects. Studies have shown that individuals with high polygenic risk scores for AF have an increased lifetime risk of developing the condition and may present with AF earlier than those with lower polygenic risk scores, independent of traditional risk factors such as age or comorbid conditions.[8,9]

Incorporating polygenic risk scores into clinical practice could aid in early risk stratification, particularly for individuals at high genetic risk who might benefit from preventive interventions.

Thromboembolism

Increased risk of thromboembolism is well reported in the patient group once AF is detected.[10,11] Since conventional scores used for risk evaluation for thromboembolic events, such as CHA_2DS_2-VASc, have proven insufficient in patients with HCM, the current standard is to initiate anticoagulant treatment as soon as AF is detected, regardless of other risk factors.[12,13]

The efficacy of direct oral anticoagulant (DOAC) treatment has been established for HCM patients with AF. Treatment with DOACs has become the main choice of anticoagulants in these patients and is preferable to warfarin due to their more predictable nature and reduced occurrence of intracranial haemorrhage.[13–15] While prevention of thromboembolism in this patient group has improved markedly, the cause of this increased risk remains a topic of debate. A popular hypothesis suspects the cause for both AF and risk of thromboembolism may be due to structural atriopathy brought about by the structural abnormalities inherent to HCM.[16] Should this connection be confirmed, new therapies aimed at treating or preventing the development of regional atriopathy could provide relief from both AF and thromboembolic risk.

Hypertrophic Cardiomyopathy, AF and Heart Failure

The onset of AF in HCM can dramatically worsen heart failure symptoms. The loss of atrial systole in a stiff ventricle reduces cardiac output and increases symptoms of heart failure. Both heart failure and AF significantly impact the prognosis and management of HCM, complicating the course of the disease and increasing overall mortality.[17] HCM, heart failure and AF create a vicious cycle. The hypertrophied and noncompliant heart muscle in HCM leads to diastolic dysfunction and left atrial enlargement, which predisposes to AF. Once AF develops, it worsens diastolic dysfunction by reducing the efficiency of ventricular filling, which in turn exacerbates heart failure symptoms.[18] Conversely, worsening heart failure can make it more difficult to manage AF, leading to more frequent and persistent episodes. Conversely, AF and other tachyarrhythmia may lead to heart failure. Adequate detection and management of both AF and heart failure are, therefore, crucial components of HCM treatment.

Hypertrophic Cardiomyopathy, AF and Sudden Cardiac Death

While AF itself is not usually directly associated with SCD, it can serve as a marker for increased risk of all-cause mortality and SCD. In patients with HCM, AF often indicates advanced disease and greater myocardial damage, which can predispose them to VAs that may lead to SCD. The structural remodelling commonly seen in HCM patients creates a substrate for both AF and SCD, as fibrosis can disrupt normal conduction pathways, facilitating both atrial and ventricular arrhythmias. HCM-related mutations often involve genes that code for sarcomere proteins, which can also affect ion channels and electrical conduction in the heart. These abnormalities increase the risk of both AF and VAs that can cause SCD. It is therefore not unreasonable to believe that AF detection might play a more prominent role in the future management of HCM patients.

Management

Management of AF in HCM patients poses unique challenges in both rhythm- and rate-control strategies. Antiarrhythmic drugs such as amiodarone and β-blockers remain common choices, though for rate control, but side-effects and tolerability limit the efficacy of these drugs. When AF develops, the loss of atrial contraction and the irregular, often rapid, ventricular response can further compromise diastolic filling, leading to a severe symptom burden. Even in cases where ventricular rate control is successfully achieved, patients may continue to experience a significant reduction in quality of life due to the combination of HCM-related diastolic dysfunction and the irregular rhythm of AF.[18,19] A rhythm control approach with catheter ablation can, therefore, be a promising option for these patients. However, here too the presence of HCM complicates management. While data remain scarce, the body of evidence does firmly support the notion that catheter ablation is less successful in patients with HCM compared with those without.[20–22] Higher recurrence rates necessitate repeat procedures and careful patient selection from treating clinicians. Despite these limitations, catheter ablation remains the most promising treatment for restoring sinus rhythm in patients with poor tolerance of symptoms. Measures aimed at increasing procedural success rates and the duration of AF-free periods will be crucial for the future advancement of catheter ablation in HCM patients, whether this is by more nuanced patient selection pre-procedure or procedural advances of catheter ablation.

Lastly, dual-chamber pacemakers, or even physiological (e.g. left bundle branch area pacing) pacing, are being explored as options to improve haemodynamics in patients with HCM who experience frequent AF episodes. Pacemakers, combined with atrioventricular node ablation, may be beneficial in refractory cases where rhythm- or rate-control with medications or catheter ablation is unsuccessful.[23]

Surgical ablation has been shown to be an effective option for rhythm control in general AF patients. While data on this topic in the context of HCM are scarce, there is some published evidence that surgical ablation may offer improved rates of rhythm control than catheter-based ablation.[24,25] This is especially the case for patients requiring surgical myectomy or surgery for valvular heart disease.

Ventricular Arrhythmias and Sudden Cardiac Death in Hypertrophic Cardiomyopathy

Individuals with HCM are particularly susceptible to VAs, ranging from single premature ventricular beats to non-sustained ventricular tachycardia (NSVT) to sustained monomorphic or polymorphic ventricular tachycardia (VT) and VF. Such VAs can, in unfortunate circumstances, even

result in cardiac arrest and SCD. Tragically, SCD predominantly occurs in children and young individuals (aged <30 years) with HCM at an incidence of about 0.5–1%.[26–28] Fortunately, clinicians can prevent this devastating fate by inserting ICDs in HCM patients as either primary prophylaxis for high-risk patients (≥6% SCD risk over 5 years in European Society of Cardiology [ESC] 2023 guidelines) or secondary prophylaxis for those who have already survived an episode of VA or cardiac arrest.

While observational studies in HCM patients have shown an overall benefit of ICDs, their efficacy is contingent on selecting the right candidates for the device based on their risk profile.[29–31] The protective effect of ICDs against SCD should be weighed against the risk of inappropriate shocks, device infections or malfunctions and competing risk of death from other causes. Since ICDs are implanted at a young age in individuals with HCM, as SCD mainly occurs in those aged <60 years, these individuals are less likely to be comorbid, yet are vulnerable to ICD complications over a longer time period.[26] Thus, it is crucial to accurately identify patients in whom the benefits outweigh the drawbacks of ICD implantation. Choice of the right type of device and custom programming to increase sensitivity in detecting and deterring arrhythmias is also essential.

Numerous guidelines and risk-stratification tools are available to support the clinician in decision-making. However, as these constantly evolve following advancements in research and technologies, it can be challenging for the clinician to stay updated. Therefore, this review will summarise the latest recommendations to help clinicians make informed, evidence-based decisions for their HCM patients.

Pathophysiology of Ventricular Arrhythmias in Hypertrophic Cardiomyopathy

Hypertrophy in HCM is mainly associated with three histopathological features: myocyte disarray, fibrosis (both replacement scarring and interstitial) and abnormal intramural vasculature.[29,32] Hypertrophied myocardium can compress intramural vasculature causing coronary artery remodelling with hypertrophy and luminal narrowing, leading to ischaemia, myocardial necrosis and fibrosis. The fibrotic changes in part resulting from microvascular ischaemia can be examined with late gadolinium enhancement (LGE) on cardiac MRI (cMRI).[32,33] Calcium sensitivity, characteristic of HCM, has also been associated with arrhythmia susceptibility.[34] These various changes provide the substrates for abnormal electrical conduction in the heart.

Monomorphic VT is presumably a result of scar-related re-entry, where anti-tachycardia pacing (ATP) by ICDs is especially effective, while VF may occur in disorganised myocardium.[33] Monomorphic VT was the most common arrhythmia in HCM patients with ICDs, followed by VF; least common was polymorphic VT.[35–37]

Sympathetic drive seems to be an influential factor as sinus tachycardia and rapidly conducted AF are often observed prior to VT or VF and could explain the phenomenon of SCDs upon exertion in athletes with HCM.[33,35]

Advances in Hypertrophic Cardiomyopathy

Recent advancements in HCM are centred around four main themes: first, optimising guidelines for identifying which HCM patients need an ICD; second, HCM management in special circumstances; third, innovation in therapies and devices; and fourth, the future of SCD risk stratification. Despite differences between European and American guidelines for HCM, both approaches show an overall convergence towards precision and personalised medicine.

Optimising Guidelines for Identifying the Hypertrophic Cardiomyopathy Patients Who Need an ICD

History of Guidelines and Risk Factors

The detection of key risk factors and modifiers of SCD in HCM patients is crucial in risk stratification to determine in which patients ICDs are indicated. Personal history (prior occurrence of VAs or cardiac arrest) conferred the highest SCD risk and, therefore, is an indication for ICDs as secondary prophylaxis.[38]

In 2003, the American College of Cardiology (ACC) and ESC in collaboration established five major non-invasive risk factors for SCD in HCM patients,[39] where the presence of at least one was a strong recommendation for ICDs as primary prophylaxis according to their expert consensus document (the stand-alone risk factor approach).[40] These risk factors are:

- Family history, i.e. one or more first-degree relatives aged <40/50 years who experienced SCD or resuscitated cardiac arrest.[3,32,41]
- Unexplained syncopes, i.e. unexplained episodes of loss of consciousness, particularly within the last 6 months.[3,40] Notably, a study found that in patients aged >40 years with unexplained syncopes more than 5 years prior, there was no increased SCD risk.[35]
- Massive left ventricular hypertrophy (LVH), which is linearly associated with risk of SCD and especially with a left ventricular wall thickness (LVWT) >30 mm.[32]
- NSVT, i.e. at least three consecutive ventricular beats during Holter monitoring with a frequency of ≤120 BPM lasting >30 seconds. NSVTs show low positive predictive value for SCD, as they are a frequent phenomenon in HCM patients aged >40 years (occurring in 20–30%). NSVTs should not stand alone in determining ICD implantation.[32]
- Abnormal blood pressure response (ABPR) to exercise, i.e. failure of a systolic blood pressure increase of >20 mmHg or a systolic blood pressure decrease of 10 mmHg during exercise. ABPR is associated with higher risk of SCD in patients aged ≤40 years, while knowledge in patients aged >40 years is lacking.[32]

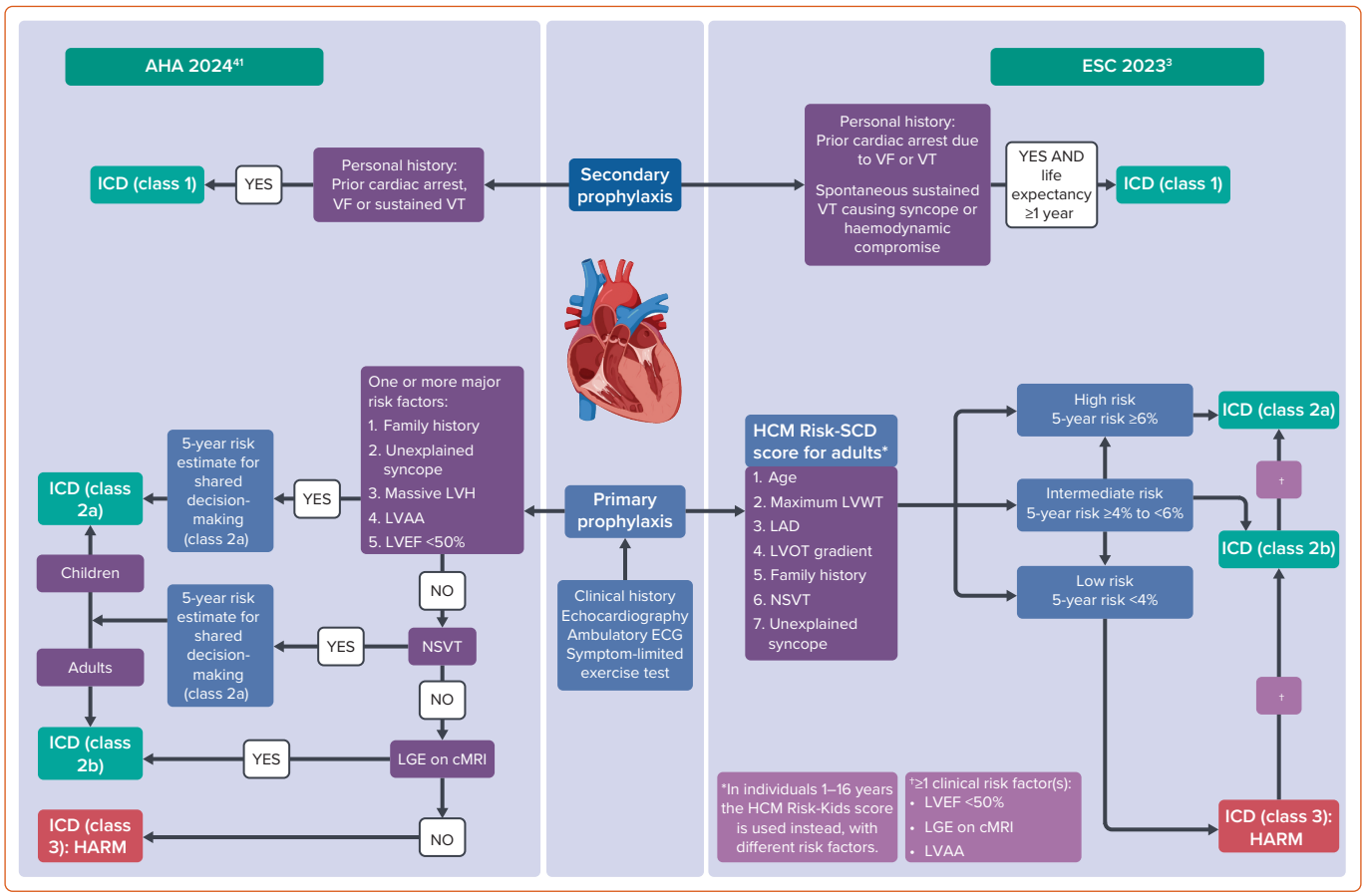
Although these risk factors showed a high negative predictive value of 95% for SCD, a low cumulative positive predictive value of only 20% led to an overestimation of SCD risk.[40] The continuous relationships between the risk factors and SCD were also not considered.[40]

Therefore, in 2014, the ESC developed the quantitative HCM Risk-SCD score.[42,43] Patients were divided into three categories of estimated 5-year risk of SCD: <4% (ICDs not recommended), 4–6% (ICDs may be considered) and ≥6% (ICDs should be considered) based on data from a statistical model showing the impact of clinical risk factors on SCD risk in large retrospective HCM cohorts.[42] The HCM Risk-SCD score added new risk factors: age, left atrial diameter (LAD) and left ventricular outflow tract (LVOT) gradient.[44,45] Statistical validation in retrospective cohorts endorsed the score against the stand-alone risk factor approach.[46–48] However, sensitivity in a real-life cohort proved limited, as SCD still occurred in patients considered low-risk in the score.[40,49]

Developments in Imaging Modalities

While echocardiography has been indispensable as a clinical tool for visualisation of cardiac infrastructure in HCM patients, it is suboptimal for the location of vulnerable substrates for VAs. LGE on cMRI is better for revealing areas of myocardial fibrosis, which was associated with higher risk of SCD in patients otherwise deemed low-risk based on traditional risk

Figure 1: Overview of Latest Guidelines for ICDs in Hypertrophic Cardiomyopathy



Family history is sudden death definitively or likely attributable to hypertrophic cardiomyopathy in one or more first-degree or close relatives aged ≤50 years. Unexplained syncope is one or more recent episodes of syncope suspected by clinical history to be arrhythmic. Massive left ventricular hypertrophy is left ventricular wall thickness ≥30 mm. AHA = American Heart Association; cMRI = cardiac MRI; ESC = European Society of Cardiology; HCM = hypertrophic cardiomyopathy; LAD = left atrial diameter; LGE = late gadolinium enhancement; LVAA = left ventricular apical aneurysm; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; LVOT = left ventricular outflow tract; LVWT = left ventricular wall thickness; NSVT = non-sustained ventricular tachycardia; SCD = sudden cardiac death; VT = ventricular tachycardia. Created with BioRender.com.

factors.[32,50] Consequently, LGE has become a pivotal tool in risk stratification and a class 1 recommendation in intermediate risk groups.[51] Presence of a left ventricular apical aneurysm (LVAA) or left ventricular systolic dysfunction (left ventricular ejection fraction [LVEF] <50%) with widespread scarring and chamber dilation also both show association with increased risk of SCD.[50]

Therefore, in 2020 American Heart Association (AHA)/ACC guidelines re-emphasised primary prophylaxis ICD implantation, even if only one risk factor was present and added LVEF <50%, LVAA and extensive LGE on cMRI as risk factors.[52,53] This approach showed higher sensitivity for SCD compared with the ESC HCM Risk-SCD score in identifying high-risk patients, yet was still unsuccessful in correctly identifying low-risk patients.[40]

Latest Guidelines for Hypertrophic Cardiomyopathy in Adults

Both the 2023 ESC guidelines and 2024 AHA guidelines state SCD risk assessment should be made at initial evaluation of HCM patients and repeated every 1–2 years or when there is a change in clinical status (class 1 recommendation). The primary distinction between the guidelines lies in the balance between prioritising sensitivity of risk stratification in predicting those who will experience SCD versus preventing unnecessary overtreatment with ICDs.[54]

Figure 1 shows an overview of the latest ESC and AHA guidelines. The 2023 ESC guidelines can be considered more conservative, with a focus on shared decision-making with the patient based on an estimated risk calculation (class 1 recommendation). Primary prophylaxis ICD implantation is a class 2a recommendation for patients aged ≥16 years (excluding elite/competitive athletes or HCM associated with metabolic diseases/syndromes) with an estimated 5-year risk of SCD ≥6% based on the HCM Risk-SCD score.[3] Then, LGE at cMRI (>15% of left ventricular mass), LVEF <50% and LVAA can be used to further discuss risks and benefits with the patient.[51]

The 2024 AHA guidelines prioritise sensitivity and suggest that in all adult HCM patients with one or more major risk factor(s) for SCD, an ICD is reasonable (class 2a recommendation).[41] For patients >16 years, class 2a recommendations state LAD and maximal LVOT gradient determined using echocardiography can be employed to estimate 5-year SCD risk.[41]

In patients not considered high risk or where the decision of ICD implantation remains uncertain after clinical assessment and echocardiography, cMRI is valuable in determining maximum LVWT, LVEF, LVAA and myocardial fibrosis using LGE. NSVT episodes on continuous ambulatory electrocardiographic monitoring can be incorporated, but with uncertain impact in the absence of other major risk factors.[41]

Latest Guidelines for Hypertrophic Cardiomyopathy in the Paediatric Population

HCM is reported to be one of the main causes of SCD in the paediatric

population, although this was not found in a Danish nationwide study.[55–57] ICD implantation should be based on different thresholds than in adults, as placement is complicated by anticipated growth of the patient and longer time for device complications to arise. Risk stratification in this group should also account for age and body size, as adult risk factors show different effects in the young. Two paediatric-specific risk models, HCM Risk-Kids (2019) and PRIMaCY (2020), have been developed and validated in young populations with similar accuracy, including age and body size.[3]

SCD risk assessment in the paediatric population should be made at initial evaluation and repeated every 1–2 years or when there is a change in clinical status (class 1 recommendation).[3]

The 2023 ESC guidelines state that in individuals aged 1–16 years with an estimated HCM Risk-Kids 5-year SCD risk ≥6%, ICD implantation should be considered. To calculate 5-year SCD risk in children with HCM, age, echocardiographic left ventricular wall z-scores, LAD z-score, maximal instantaneous LVOT gradient with continuous-wave Doppler technique, history of unexplained syncope and NSVT, with or without genotype status, are used.[3]

The 2024 AHA guidelines state that ICD implantation is reasonable in children with HCM with one or more major risk factors for SCD of family history, unexplained syncope, massive LVH or NSVT.[41] In borderline patients, cMRI can be useful to determine LGE, yet involves sedation and the risk associated with this.[41] Class 2a recommendations state an estimated 5-year SCD risk using echocardiographic parameters (LAD, maximal LVOT gradient, interventricular septal thickness in diastole, left ventricular posterior wall thickness in end-diastole) and genotype to be useful in a shared decision-making process.[41]

Shared Decision-making

Both ESC and AHA guidelines can be integrated by considering both an estimated 5-year SCD risk score based on HCM Risk-SCD or HCM Risk-Kids and major risk factors and then discussing these along with mortality rates with an informed patient and family. In the end, the decision to implant an ICD is, in most countries, a shared decision-making approach with the patient instead of simply following prespecified risk thresholds, as individual patients may consider risk estimates differently. The impacts of LVAA, LGE and LVEF <50% on risk estimates also remain unclear, thus should be discussed together with the family.[41] Other factors relevant to consider include alcohol septal ablation, competitive sports participation, coronary artery disease, socioeconomics, patient comorbidities, impacts on lifestyle and psychosocial impacts of ICD therapy.[41,50]

Hypertrophic Cardiomyopathy Management in Special Circumstances

Management in Pregnancy

Pregnant women with HCM show low maternal mortality, with symptoms and complications primarily appearing in those with pre-existing symptoms.[41] Nonetheless, multidisciplinary teams including cardiologists, obstetricians and anaesthetists are a crucial component of care. Pre-pregnancy risk assessment using WHO classification allows for discussion of maternal risk and outcomes, medications, pregnancy care and delivery plans. High-risk cases may require consultation with maternal–foetal medicine experts.[41]

For very symptomatic women, preconception interventions to reduce risk could be septal reduction therapies (SRT) for medically refractory symptomatic LVOT obstruction (LVOTO) or advanced heart failure therapies.[41] ICDs or catheter ablation should be considered preconception or 8 weeks beyond gestation with radiation protection. Pregnant patients with ICDs require routine check-ups and advice prior to delivery.[3]

Preconception counselling is recommended, including preimplantation genetic testing, foetal screening, prenatal testing and foetal echocardiography. During pregnancy, serial echocardiography, particularly in second and third trimesters or if clinical symptoms develop, is advised because of increased haemodynamic demands.[41]

Medications should be checked for safety prior to pregnancy and offered at the lowest effective dose. Vitamin K antagonists and low-molecular-weight heparin are recommended for those requiring anticoagulation (e.g. with AF), as DOACs showed higher rates of foetal complications in a meta-analysis.[3,41] In symptomatic AF, cardioversion can be performed during pregnancy with minimal foetal risk. β-blockers (except atenolol) can be continued with careful monitoring of foetal growth and foetal bradycardia. Myosin inhibitors, including mavacamten, are contraindicated because of potential teratogenic effects.[3,41]

Vaginal delivery is preferred, unless caesarean section is indicated for obstetric reasons, severe LVOTO, heart failure, high arrhythmic risk or use of anticoagulation. Spinal and epidural anaesthesia can be used with precautions to avoid hypotension. The first 24–48 hours postpartum pose a high risk for heart failure, requiring close monitoring. Breastfeeding may be contraindicated based on maternal medications.[3,41]

Management During Electrical Storms

Electrical storms are severe presentations of VAs and a cardiac emergency, defined as three or more episodes of sustained VT, VF or appropriate shocks from an ICD over 24 hours. During an electrical storm, ICDs may provide multiple shocks, both uncomfortable for patients and likely unsuccessful in preventing further arrhythmia episodes. Intravenous administration of antiarrhythmic drugs, such as amiodarone or β-blockers, can stabilise the patient's rhythm. Sedation can also reduce psychological distress, sympathetic drive and arrhythmia burden.[58]

If the electrical storm persists, deep sedation or intubation can be attempted. Other options include catheter ablation or autonomic modulation via stellate ganglion block or sympathetic denervation. Mechanical circulatory support, e.g. veno-arterial extracorporeal membrane oxygenation may be necessary for haemodynamic stabilisation. Alternative strategies include resection of apical aneurysms and endocardial scarring to reduce risk of VAs. As a last resort, orthotopic heart transplantation may be considered.[58]

Innovation in Therapies and Devices

Therapeutic Strategies

Previously, treatment options for HCM primarily focused on non-specific medications such as β-blockers, amiodarone, verapamil or disopyramide.[33,40] Myosin inhibitors, such as mavacamten, are novel drugs with great promise in obstructive HCM, as they more specifically target pathophysiological mechanisms in HCM.[59–62] The therapies involve a small-molecule allosteric inhibition of cardiac myosin, and effects upon reducing LVOTO have been shown in both preclinical and randomised controlled trials.[57,60]

Therefore, in adult patients with obstructive HCM showing persistent symptoms due to LVOTO despite β-blockers and non-dihydropyridine

calcium channel blockers, myosin inhibitors are now a class 1 recommendation in the 2024 AHA guidelines alongside disopyramide (in combination with an atrioventricular nodal blocking agent) or SRT performed at experienced centres. However, the long-term safety, efficacy and effects on SCD risk of myosin inhibitors are yet to be established in upcoming studies.[41] Myosin inhibitors could, perhaps in the future, be incorporated in risk models for SCD involving LVOT gradient.

SRTs such as surgical septal myomectomy and alcohol septal ablation are recommended at specialised centres in the latest AHA and ESC guidelines for drug-refractory cases or severe LVOTO. In HCM patients with symptomatic VAs or recurrent ICD shocks despite β-blockers, antiarrhythmic drug therapy with amiodarone, dofetilide, mexiletine or sotalol is recommended. In advanced heart failure or patients with recurrent life-threatening arrhythmias despite maximal antiarrhythmic drug therapy and ablation, heart transplantation is a final option.[41]

Subcutaneous ICDs

As patients with HCM have ICDs implanted at a young age, and many have concomitant AF, they are at a higher risk of ICD-related complications and inappropriate shocks. Therefore, as opposed to the traditional single chamber transvenous ICD (TV-ICD), a subcutaneous ICD (S-ICD) seems to be a safe and effective alternative.[63]

S-ICDs were a class 2a recommendation in the 2023 ESC guidelines as an alternative when pacing therapy for bradycardia, cardiac resynchronisation or ATP is not anticipated, yet their long-term efficacy and safety are yet to be determined.[3] The PRAETORIAN trial demonstrated fewer lead-related complications and systemic infections with the S-ICD compared to the TV-ICD, and the occurrence of inappropriate shocks was not statistically different.[63–65] In the 2024 AHA guidelines, S-ICDs have been upgraded to a class 1 recommendation.[41]

ATP can occasionally terminate VAs and circumvent the need for painful shock therapy from ICDs. The most common arrhythmia in HCM patients with ICDs was found to be sustained monomorphic VT, particularly receptive to ATP.[35] However, S-ICDs are contraindicated in patients requiring ATP, as they cannot provide it.[28,35] Therefore, the MODULAR ATP study investigated performance of a modular pacing-defibrillator system, i.e. a S-ICD in wireless communication with a leadless pacemaker that can provide ATP, showing successful ATP termination of arrhythmias.[66] This system is an anticipated option for HCM patients with S-ICDs.

The Future of Sudden Cardiac Death Risk Stratification

Studies have shown B-type natriuretic peptide levels and concomitant AF could impact SCD risk in HCM patients and thus may be incorporated in risk models in the future.[2,67,68]

Genetic testing is under investigation as a valuable addition to risk stratification for SCD. Currently, genotype-positive, phenotype-negative HCM patients are not recommended an ICD.[41] Yet, some studies suggest that sarcomere mutations have been associated with higher risk of SCD in HCM patients.[69–71] However, varying penetrance and phenotype seen in families harbouring the same sarcomere mutation render it yet unclear whether incorporating genetic status would improve adult risk stratification.[33,70] As there is evidence for the presence of multiple sarcomere mutations being a risk factor for SCD, this could instead act as a risk modifier in ICD implantation evaluation.[71] Although genotype-positive status has been associated with higher SCD risk in children with HCM, it has not yet been included as a formal risk factor in risk models for children.[72]

However, advances in precision and personalised medicine extend far beyond genetic testing. Human myocardial samples from surgery and transgenic animal models can be used to evaluate the impacts of genetic mutations on arrhythmogenic propensity.[26] CRISPR-Cas9 could be used to introduce or correct genetic mutations to investigate impacts on cardiomyocyte function.[73] Human induced pluripotent stem cells-cardiomyocyte testing also shows promise in patient-specific disease modelling to comprehend arrhythmogenic mechanisms and, thereby, treatment options, yet currently may not accurately depict adult heart-cell functions.[74] The introduction of 3D culture systems is working to address this issue.[75]

Finally, machine learning can integrate data from multiple modalities and improve risk stratification by identifying complex patterns and interactions between risk factors and could enable better prediction than the current HCM Risk-SCD tool.[76] These are all exciting upcoming areas with great potential to enhance risk stratification in patients with HCM.[32]

Conclusion

In summary, HCM presents complex clinical challenges, particularly regarding arrhythmia management and SCD prevention. Recent advancements in genetic testing, imaging and risk stratification tools, along with novel therapies such as myosin inhibitors, have transformed patient care and enabled more targeted management approaches. However, significant gaps remain in understanding the arrhythmogenic mechanisms and optimal intervention strategies, especially for patients with refractory arrhythmias. On-going research is essential to refine risk prediction, improve therapeutic outcomes and provide tailored solutions that address both arrhythmic and structural cardiac risks in HCM. ❑

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