Chapter

ICD for Sudden Cardiac Death Prevention and New Pharmaceutical Treatment Options in Hypertrophic Obstructive Cardiomyopathy

Antonio da Silva Menezes Junior, Thais Aratak Marques Taia, Camila Cássia Canzi, Ana Lígia Valeriano de Oliveira, Lucas Eduardo Almeida França, Aline Lins da Silva, Matheus Araújo Borges and Guilherme Diniz Prudente

Abstract

In humans, hypertrophic cardiomyopathy (HCM) is a heterogeneous cardiac illness typically caused by autosomal dominant sarcomeric gene mutations and characterized by reduced heart's compliance, myofibrillar disarray, and fibrosis of the heart. Areas covered: Although HCM was formerly viewed as a malignant disease entity with few treatment choices, effective management strategies have emerged so that affected individuals may expect to have a normal lifespan without the need for pacing or another type of invasive intervention. Herein, these management strategies are discussed. There is no curative treatment for HCM that reverses or prevents hypertrophy and heart dysfunction. Drug-based therapies aim to alleviate its symptoms and slow disease progression. Mavacamten is a reversible cardiac myosin allosteric modulator with a potential therapeutic effect for obstructive HCM. Mavacamten markedly improved the health status of patients with symptomatic obstructive hypertrophic cardiomyopathy compared with a placebo. In patients with HOCM, the importance of an implantable cardioverter defibrillators (ICD) is to prevent sudden cardiac death (SCD). Approximately 25% of those with HCM suffer from atrial arrhythmias, and the condition is notoriously difficult to manage. Anti-arrhythmic drugs, such as sotalol, amiodarone, and disopyramide, are routinely prescribed. Radiofrequency ablations for atrial fibrillation in patients with HCM have become more common despite their limited effectiveness (about 70% recurrence).

Keywords: obstructive hypertrophic cardiomyopathy, implantable cardioverter Desfibrillator, sudden cardiac death, pharmaceutical treatment, prevention

1. Introduction

In humans, hypertrophic cardiomyopathy (HCM) is a common (1:500 – general population) autosomal dominant inherited cardiovascular disease. It is caused by more than 1400 mutations in 11 or more genes encoding proteins of the cardiac sarcomere. HCM is characterized by left ventricular (LV) hypertrophy, myocardial hypercontractility, and other cardiac abnormalities. Reduced compliance, myofibrillar disarray, and fibrosis are all fenotypes of HCM [1, 2].

Even though HCM was formerly seen as a bleak, unyielding, and malignant disease entity with few treatment choices, the clinical story of the illness has dramatically transformed in recent years. Improved clinical recognition, including benign low-risk subgroups without significant symptoms or disability [3] has led to effective management strategies for major HCM complications, resulting in significantly lower mortality and morbidity rates. Affected individuals have an increased likelihood of achieving normal longevity into their 70s to 90s or even later with good quality of life [3].

Patients with LV dysfunction, obstruction of the left ventricular outflow tract (LVOT), and mitral regurgitation (MR) may have impaired exercise capacity, as well as exertional dyspnea and chest discomfort and syncope. Microvascular dysfunction and subendocardial ischemia are the underlying causes of these symptoms. Septal hypertrophy, as well as issues with the mitral valve and subvalvular apparatus, contribute to systolic anterior motion (SAM) and obstruction of the LVOT, resulting in obstructive HCM (HOCM), as seen in **Table 1**.

2. Implantable defibrillator cardioverter

Implantable cardioverter defibrillators (ICDs), composed of a defibrillator and electrodes, avoid ventricular arrhythmias and sudden death. The American Heart Association (AHA) and the European Society of Cardiology (ESC) recommend ICDs as a secondary preventive measure for patients with hemodynamically severe ventricular arrhythmias or prior cardiac arrests, as seen in **Table 2** and **Figure 1** [4].

Studies demonstrate that an ICD helps individuals who have had cardiac arrests and slows the progression of HCM by averting sudden death [1, 2]. In patients with HOCM, biventricular implanted cardio defibrillators reduce obstruction in the LVOT, indicating that they improve systolic function in the left ventricle [5].

Thavikulwat et al. studied adult patients with HCM treated with ICD at the Cardiovascular Institute of Bluhm from 2000 to 2013 to assess risk factor profiles, ICD treatment rates, and consequences [4]. During the 5.2-year period, 25 of the 135 patients treated received ICDs. No statistically significant difference was observed between individuals who died suddenly and those who did not undergo ICD therapy. While younger ICD patients received more suitable care, 20% of these patients had insufficient therapy.

Maron et al. [5] studied 486 individuals with high-risk HCM from eight worldwide sites. Among them, 19% received ICD intervention due to ventricular tachycardia or fibrillation. Only one patient died suddenly from ICD failure, while three others died from causes connected to HCM but unrelated to the arrhythmogenic effect. Although anticipation of future shocks increased anxiety, individuals who received any ICD intervention showed no HCM mortality in 1, 5, and 10 years [5]. Notably, ICD was not associated with an increase in mortality, cardiovascular

Structural Derangements	Molecular Derangements	Novel Procedures	Novel Pharmacotherapies	Gene-Based Therapies	Genetic Derangements
Septal hypertrophy	Actin-myosin cross-bridging	Surgical papillary muscle realignment, chordae removal, and mitral valve repair	Mavacamten, CK-274	Allele-specific gene silencing	Genetic mutations in sarcomeric proteins
Mitral leaflet abnormalities	Myocardial metabolism Sodium and calcium channels	Apical myectomy	Perhexiline, trimetazidine ranolazine, eleclazine N-acetylcysteine ARBs, aldosterone antagonists	Embryonic gene repair using CRISPR/ Cas9	—
Subvalvular abnormalities	Hyperdynamic L function, impaired LV relaxation and compliance	Transcatheter mitral valve repair	Statins	—	—
SAM/LOT obstruction	Myocardial disarray, fibrosis, and adverse remodeling	Radiofrequency septal ablation	—	—	—
Mitral regurgitation	—	High-intensity focused ultrasound septal ablation	—	—	—

Novel procedural approaches target cardiac structural abnormalities in hypertrophic cardiomyopathy. Novel pharmacotherapies target abnormal cellular processes in hypertrophic cardiomyopathy. Allele-specific gene silencing and genome editing using CRISPR/Cas9 target the genetic underpinnings of hypertrophic cardiomyopathy. ARB, angiotensin II receptor blocker; LV, left ventricular; LVOT, left ventricular outflow tract; SAM, systolic anterior motion. Source: Tuohy CV, Kaul S, Song HK, Nazer B, Heitner SB. Hypertrophic cardiomyopathy: the future of treatment. Eur J Heart Fail. 2020;22(2):228–240. doi:10.1002/ejhf.1715 Order Date12-May-2022/Order License ID1220726–1/ISSN1388–9842.

Table 1.
Novel therapeutic targets in hypertrophic cardiomyopathy.

Class of recommendation	Recommendations
1 – Strong	In patients with HCM, individualization is recommended, with prognostic analysis of conventional risk markers, clinical profile, and balanced discussion of evidence, risks, and benefits, involving the patient actively in the decision-making process for implantation of the ICD.
1 – Strong	ICD implantation is recommended in patients with HCM and a history of documented cardiac arrest or sustained ventricular tachycardia (VT)
2ª – Moderate	It is reasonable to offer an ICD implant to adult patients with HCM with ≥1 major risk factor, as listed below, for sudden cardiac death. a. Sudden cardiac death judged definitive or likely attributed to HCM in ≥1 first-degree relatives or close relatives aged ≤50 years. b. Massive LVH ≥30 mm in any left ventricular (LV) segment; c. Presence of ≥1 suspicious episode of syncope, such that its origin is neurocardiogenic (vasovagal) or related to Left ventricular outflow tract obstruction (LVOTO); d. LV apical aneurysm, independent of size; e. LV systolic dysfunction (EF <50%).
2ª – Moderate	ICD implantation becomes reasonable in children with HCM with ≥1 conventional risk factor, including unexplained syncope, massive LVH, NSTV, or family history of HCM related to early sudden cardiac death (SCD);
2ª – Moderate	For patients≥16 years of age with HCM and with ≥1 major SCD risk factor, discussion of the estimated 5-year risk of sudden cardiac death and mortality rates may prove helpful during the shared decision-making process for placement of the CDI
2b – Weak	Selected adult patients who have HCM and do not have risk factors for sudden cardiac death after clinical evaluation, or in whom the decision to proceed with ICD implantation still remains uncertain, ICD can be considered in patients with extensive Late Gadolinium Enhancement (LGE) by cardiac magnetic resonance (CMR) or nonsustained ventricular tachycardia (NSTV) present on ambulatory monitoring
2b – Weak	For selected pediatric patients with HCM and uncertain risk stratification, it may be worth considering additional factors such as extensive Late Gadolinium Enhancement (LGE) on cardiovascular magnetic resonance imaging (CMR) and systolic dysfunction in risk stratification
3 – Harm	ICD placement should not be performed in patients with HCM without risk factors
3 – Harm	In patients with HCM, ICD placement for the sole purpose of participation in competitive athletics should not be performed

The original source was adapted from the authors. "Ommen SR, Mital S, Burke MA, Day SM, Deswal A, Elliott P, et al. 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients with Hypertrophic Cardiomyopathy: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Vol. 142, Circulation. Lippincott Williams and Wilkins; 2020. p. E533–57."

Table 2.
Eligibility criteria for ICD implementation.

morbidity, or worsening heart failure. Furthermore, although it causes worry in people who have previously received ICD intervention, it does not significantly affect their psychological well-being [5].

Giraldeau et al., despite studying a small sample, assessed the effectiveness of biventricular stimulation (BiV) in 13 individuals (average age of 55 years) with

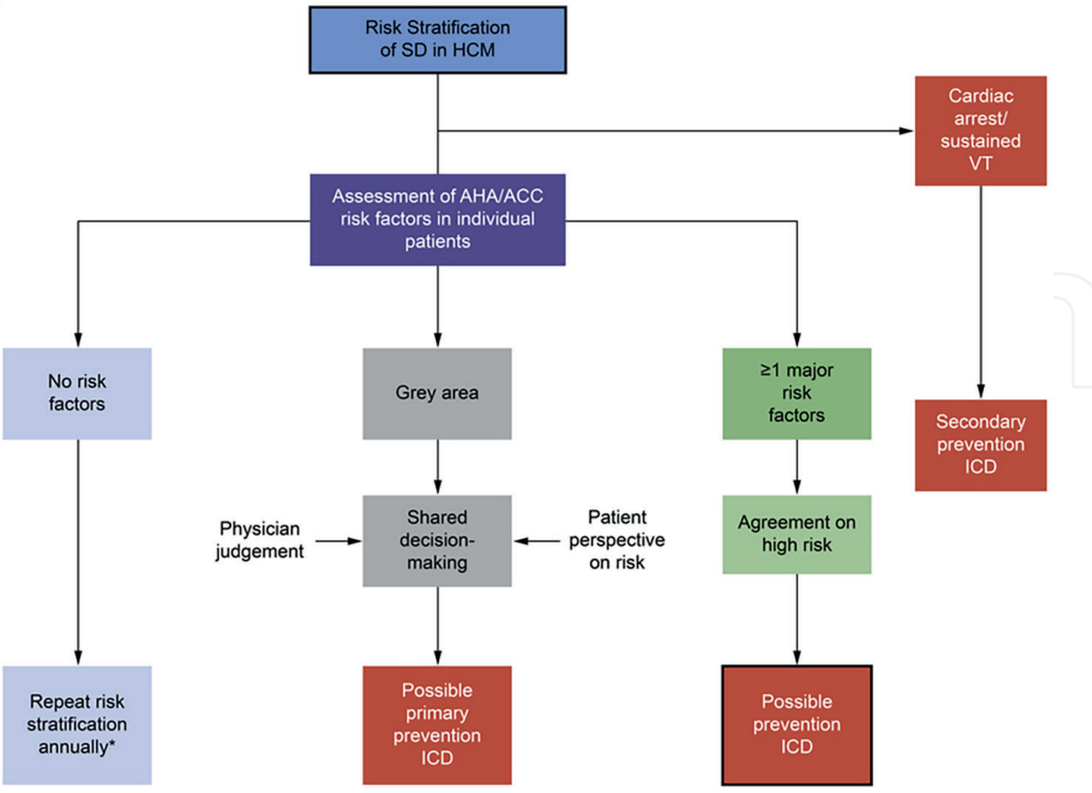

Figure 1.
Risk stratification of SD in HCM. HCM = hypertrophic cardiomyopathy; ICD = implantable cardioverter defibrillator; SD = sudden death; VT = ventricular tachycardia. Source: Maron BJ, Desai MY, Nishimura RA, et al. Management of Hypertrophic Cardiomyopathy: JACC state-of-the-art review. J Am Coll Cardiol. 2022; 79:390–414. This agreement between Antonio da Silva Menezes junior ("You") and Elsevier ("Elsevier") consists of your license details and the terms and conditions provided by Elsevier and copyright clearance center. License number 5305400128072 license date may 10, 2022.

HOCM who had undergone 2D transthoracic echocardiography before implantation and were followed for 12 months [6]. The peak gradient in the LVOT was lowered from 80 to 30 mmHg. Displacement curve analysis revealed an inversion of lateral wall movement time in these individuals, with a reduced LVOT gradient. The study concluded that BiV reduces LVL obstruction in patients with HOCM by desynchronizing LV movement and inverting the activation time of the LV wall, without affecting the LV's systolic function [6].

To diagnose, confirm, or stratify the type of hypertrophy present in individuals with HCM, Freitas et al. conducted a multicentric retrospective investigation of 493 patients (58% male; mean age of 46 years) [7]. Their goal was to prove that cardiovascular magnetic resonance imaging and late gadolinium enhancement may be used to stratify risk. The sudden death risk score for HCM and the algorithms of the American College of Cardiology Foundation and the American Association of Cardiology (ACCF/AHA) were used to determine individuals' eligibility for ICDs. During the median 3.4-year follow-up, 12 patients died, 6 had adequate ICD discharges, and 5 had prolonged ventricular tachycardia. Compared to ratings and algorithms, late gadolinium enhancement was the sole independent predictor of outcomes. As people with HCM are more prone to unexpected death, this tool is vital.

Aducci et al. [8] studied 77 patients (45 male, mean age of 46 years) with HCM who received a transvenous ICD. In total, 24 of the patients experienced 49 episodes

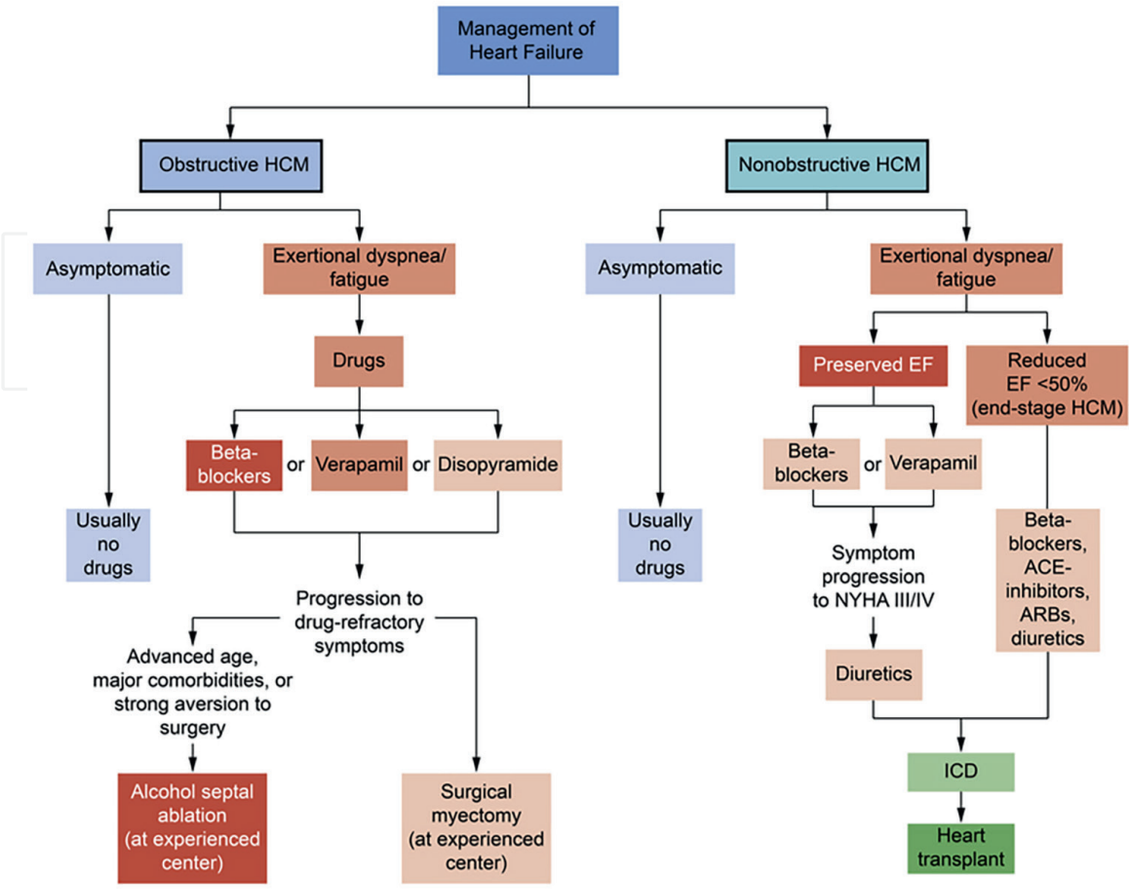

Figure 2.
Management strategies for HCM. HCM = hypertrophic cardiomyopathy; ICD = implantable cardioverter defibrillator; SD = sudden death; VT = ventricular tachycardia. Source: Maron BJ, Desai MY, Nishimura RA, et al. Management of Hypertrophic Cardiomyopathy: JACC state-of-the-art review. J Am Coll Cardiol. 2022; 79:390–414. This agreement between Antonio da Silva Menezes junior ("You") and Elsevier ("Elsevier") consists of your license details and the terms and conditions provided by Elsevier and copyright clearance center. License number 5305400128072 license date may 10, 2022.

of ventricular tachycardia/fibrillation after 67 months. Antitachycardia pacing (ATP) by ICD was successful in 69% of 39 monomorphic ventricular tachycardia (VT) events. However, even with ATP, two episodes of VT occurred. [8]. Thus, although ATP is relatively successful in treating monomorphic VTs in patients with HCM, its optimal treatment rate remains low, and it is typically provided prematurely, raising concerns about arrhythmia induced by ATP [8].

Between June 2014 and May 2016, Maurizi et al. [9] studied 50 patients (34 males; mean age of 40 years; body mass index [BMI] of 25.2) with HCM referred for subcutaneous ICD implantation in primary and secondary preventive centers in seven Italian locations. VT occurred in seven individuals and was cardioverted in two cases. The remaining patients experienced 73 bouts of ventricular fibrillation, with 6% spontaneous conversion. Defibrillation failed in only one patient, who was significantly obese (BMI of 36) and had a maximal LV wall thickness of 25 mm [9].

As reported by the AHA, the 65 J acute defibrillation test with subcutaneous ICD detects and stops VT in 98% of people. Severe obesity is the cause of lone failure (9). These recommendations and/or the ESC's HCM sudden cardiac death (SCD) risk calculator is used to determine if an ICD should be used in a patient at risk for SCD. Late gadolinium enhancement on cardiac magnetic resonance imaging, LV

systolic dysfunction, and LV apical aneurysm have all been included in an American College of Cardiology (ACC)/AHA risk stratification strategy that has recently shown improved discrimination for SCD or appropriate ICD therapies, as seen in **Figure 2**. However, this much more conservative approach would lead to significantly higher ICD utilization [10–17].

From January 2005 to September 2016, Valzania et al. studied 99 patients (mean age of 53 years) with HCM who received an ICD at Karolinska University Hospital. In follow-up, 12 died from heart failure (HF), 6 from SCD, and 6 from other causes; 20% of the patients demonstrated occlusion of the LVOT due to HOCM, and primary prevention was the top indication for an ICD [10–12].

Apart from septal reduction treatment, people with HCM may expect to have a normal lifespan without the need for pacing, which is indicated only when LVOTO is present. As a result, the subcutaneous implantable cardioverter defibrillator (S-ICD; Boston Scientific, Minneapolis, MN, USA) has become a viable option for both primary and secondary prevention of SCD. Due to the sensing mechanism of the S-ICD's three subcutaneous vectors, QRS and T-wave anomalies in young patients pose constraints—prescreening failure rates for patients with HCM range from 14–38% due to T-waver sensing. However, shocks might still be inappropriate in 8–24% of patients even after proper screening; inappropriate shocks can occur due to factors such as the need for reprogramming and muscle noise due to myopotentials [58]. Therefore, cautious patient selection is required [9, 10].

In patients with HOCM, the importance of an ICD is to avoid SCD (DDD ICD with a lead placed into RVA and programmed short AV-delay). Approximately 25% of those with HCM suffer from atrial arrhythmias, and the condition is notoriously difficult to manage. Anti-arrhythmic drugs, such as sotalol, amiodarone, and disopyramide, are routinely prescribed. Radiofrequency ablations for atrial fibrillation in patients with HCM have become more common despite their limited effectiveness (about 70% recurrence over 3–4 years after a single treatment). Myectomy surgery may be somewhat more successful than surgical ablation at the time of the procedure (recurrence rate of 36–51%), as seen in **Figure 2** [10–13].

3. Novel drugs for HCM

There is no curative treatment for HCM that reverses or prevents hypertrophy and heart dysfunction, but there are therapeutic options that can generate less progression and greater relief of symptoms. Therefore, drug-based therapies are aimed at alleviating the symptoms associated with HCM and slowing disease progression. Patients with HCM who are symptomatic are generally offered first-line pharmacotherapy with β-blockers or nondihydropyridine calcium channel blockers. Disopyramide is effective as an add-on therapy, although it can be poorly tolerated. The inotropic effects of these drugs have been the cornerstone of therapy for decades, reducing SAM/septal contact and LVOT occlusion. However, existing guideline-directed pharmacotherapies were never developed for the treatment of HCM, and lack of evidence. Further, randomized studies have not shown the superiority of any treatment over that of the placebo, based on a small study performed in 1966 [13]. Nonobstructive HCM (noHCM), which accounts for about 30% of all cases of HCM, remains poorly understood and has no recognized disease-modifying therapy. Studies have shown significant disparities in the presentation of HCM between men and women, with the latter being older and more symptomatic at the

time of diagnosis, as well as perhaps having a poorer overall survival rate than the former [14–35].

3.1 Mavacantem and Aficatem (CK-274)

Mavacantem is a reversible cardiac myosin allosteric modulator that has a potential therapeutic effect for individuals with (HOCM). This modulator demonstrated significant mitigation of hypercontractility, ventricular hypertrophy, myofibrillar disarrangement, and fibrosis in animal models [35–42].

Patients with HCM were treated with mavacamten for 12 weeks, which resulted in a quick and significant decrease in the gradient (LVOT) following exercise in the study participants. Patients with plasma mavacamten concentrations between 350 ng/mL and 700 ng/mL were more likely to have a VSVE gradient of less than 30 mmHg (the threshold for obstruction in HCM) and less than 50 mmHg (the threshold for consideration of septal reduction therapy) than those with lower values. Such an event is probably due to the fact that mavacamten acts to reduce the formation of actin-myosin cross-bridges, thus generating less systolic and diastolic cross-bridge formation. In addition, it promotes a relaxed energy-saving state that reduces LVOT obstruction [20]. A clinically significant improvement in symptoms, particularly dyspnea, as well as increased effort capacity, was also observed [43, 44]. At the end of the 12-week research, mavacamten lowered the mean gradient of postexercise VSVE from 103 mmHg (standard deviation, 50) at baseline to 19 mmHg (standard deviation, 13; mean change, −89.5 mmHg; 95% confidence interval [CI], −138.3 to - 40.7 mm Hg; P = 0.008). The LVEF at rest was also decreased (mean variation, −15%; CI, −23% to −6%), while peak oxygen consumption rose by an average of 3.5 mL/kg/min (CI 1.2 to 5.9 mL/kg/min) [43–45].

While this modulator was well tolerated by patients at exposures that successfully decreased VSVE obstruction, decreases in LVEF that were greater than those required to alleviate VESV obstruction were shown to be irreversible. Lowered LVEF at higher plasma concentrations and atrial fibrillation (AF) were the most prevalent adverse events conclusively or probably associated with mavacamten use [45].

Several characteristics of HCM were demonstrated by Prondzynski et al. [46], including hypertrophy, myofibrillar disarray, hypercontractility, impaired relaxation, and increased myofilament mass. They also demonstrated that cardiomyocytes derived from human induced pluripotent stem cells and manipulated cardiac tissues recapitulated several characteristics of HCM, including prolongation of the duration of the action potential and increase in myofilament, among others. As a result of these differences, the current density of calcium channel type L was greater in those with HCM than in the control group, as was the duration of the action potential. In addition to the above, this study revealed a novel HCM mutation that was associated with a contractile and electrophysiological phenotype in hiPSC-derived cardiomyocytes [46, 48, 49–56].

It was revealed via the optimization of the indoline compound that aficamten (CK-274), a new cardiac myosin inhibitor, could be developed. Among the most significant advancements in the optimization process was the identification of an Indane analog, which is a molecule that presents an attractive biological profile for the development of therapeutic molecules, in such a way that having a less restricted structure-activity relationship and allowing the fast development of drug-like characteristics. Aficamten was developed to have a predicted human

half-life (t1/2) appropriate for once daily (od) dosing, to reach a steady state in less than two weeks, to cause no significant cytochrome P450 induction or inhibition, and to have a broad therapeutic window in vivo with a clear pharmacokinetic/pharmacodynamic relationship, among other characteristics. Aficamten displayed a human t1/2 that was comparable to projections in the phase I clinical study, and it was able to achieve steady state concentration within the two-week timeframe that had been set [57].

With an estimated human half-life of two weeks and no significant CYP induction or inhibition in preclinical studies, aficamten offers an attractive therapeutic window and a clear PK/PD connection. The large therapeutic window reported in preclinical trials seems to apply to people, supporting the development of aficamten into phase 1 investigations. Aficamten may help reduce cardiac sarcomere hypercontractility, which seems to cause pathological hypertrophy, outflow obstruction, and fibrosis in some hereditary hypertrophic cardiomyopathies [57–59].

4. Conclusions

There is no curative treatment for HCM that reverses or prevents hypertrophy and heart dysfunction; therefore, drug-based therapies are aimed at alleviating the symptoms associated with HCM and slowing disease progression. Notably, ICD is beneficial for the prevention of SCD, as it is not associated with an increase in mortality, cardiovascular morbidity, or worsening of HF. While people who have previously experienced some type of ICD intervention express anxiety, it does not significantly affect their psychological well-being.

In certain cases, implanting ICDs is a difficult choice to make, particularly when the available information is insufficient to appropriately classify a patient's risk level. To resolve the doubt, a thorough physician's clinical judgment/intuition and medical reasoning, as well as frank discussions with fully informed patients and families, considering the benefits and limitations of risk stratification and ICDs, may be beneficial. In this approach, the different personal views of patients about sudden death risk and implanted gadgets, as well as opinions from other countries and cultures, are to be considered. The risk of sudden death in HCM is the same for men and women of any race or gender, although ICDs are less often used in minorities than in majority populations.

A successful treatment/prevention of life-threatening ventricular arrhythmias in the HCM population has been proven despite the severe morphology typical of HCM, which often includes large degrees of left ventricular hypertrophy and/or LV outflow tract obstruction. A high incidence of appropriate intervention was seen in studies of individuals judged to be at high risk, both in secondary prevention and in primary prevention, the researchers found. It is even more remarkable that this adequate intervention rate is achieved even considering the young and generally healthy individuals that make up the HCM population.

Because the incidence of SCD in HCM is very low, it is critical to identify individuals who are at high risk of SCD. Traditional risk classification strategies based on clinical risk variables have significant drawbacks and have been shown to overestimate the level of risk. Compared to standard risk prediction models based on bivariate risk variables, a novel risk prediction model that delivers individual 5-year projected risk seems to be better. Preoperative problems seem to be comparable to those associated with the placement of other cardiac devices, but

long-term consequences have typically been the focus of research and discussion. Because of their young age at implant and higher frequency of atrial fibrillation, HCM patients are assumed to be more prone to ICD-related issues and inappropriate ICD treatment. However, long-term follow-up evidence on ICD-related complications in general practice is sparse.

Conflict of interest

The authors declare no conflict of interest.

Author details

Antonio da Silva Menezes Junior*, Thais Aratak Marques Taia, Camila Cássia Canzi, Ana Lígia Valeriano de Oliveira, Lucas Eduardo Almeida França, Aline Lins da Silva, Matheus Araújo Borges and Guilherme Diniz Prudente
Medical and Life School Goiânia, Pontifical Catholic University of Goiás, Goiás, Brazil

*Address all correspondence to: a.menezes.junior@uol.com.br

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