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Stage-specific therapy for hypertrophic cardiomyopathy

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Hypertrophic cardiomyopathy (HCM) is the most common inherited myocardial disease and is defined by otherwise unexplained left ventricular hypertrophy. The main complications include heart failure and arrhythmias such as atrial fibrillation and ventricular arrhythmias. Current treatment rests on septal reduction therapies, prevention of sudden cardiac death through implantable cardioverter defibrillator, and use of drugs such as beta-blockers, calcium antagonists, or amiodarone. In the last years, new pharmacological agents specifically targeting the pathophysiology of the disease have been developed with encouraging results in terms of functional capacity and symptoms improvement from clinical trials. In this review, we summarize the possible treatment approaches for each phase of the natural history of the disease: pre-phenotype expression, classic phenotype, adverse remodelling, and overt dysfunction.

Introduction

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiomyopathy with a prevalence in the general population of 1:500. It is defined by left ventricular (LV) hypertrophy otherwise unexplained by other conditions with a maximal end-diastolic wall thickness of ≥15 or ≥13 mm in familial cases. The condition is often caused by variants in the genes encoding for sarcomere proteins, most commonly MYH7 and MYBPC3. The penetrance of HCM is variable and the phenotype extremely diverse even within family members carrying the same pathogenic mutation. The main complications include LV outflow tract or midventricular obstruction, heart failure (HF), atrial fibrillation (AF), ventricular arrhythmias, and sudden cardiac death (SCD). Current treatment rests on septal reduction therapies (SRT), the implantable cardioverter defibrillator (ICD), and time-honoured use of drugs developed for other purposes, such as beta-blockers (BBs), calcium antagonists, or amiodarone. In the last few years, however, novel drugs aimed at specific pathophysiologic mechanisms of HCM have been developed. As this new era begins, many gaps in knowledge remain regarding the optimal pharmacological management of this complex disease. Importantly, treatment targets change substantially with the evolving natural history and clinical manifestation of each patient, so that accurate staging of HCM becomes key in decision-making —an aspect often overlooked in clinical practice. In this paper, we will therefore review old and new drugs in relation to the different phases of the natural history of the disease, as previously proposed by our group: pre-phenotype expression, classic phenotype, adverse remodelling, and overt dysfunction (*Figures 1* and *2*).[1]

Stage 1: pre-phenotype expression and prevention of hypertrophic cardiomyopathy development

Widespread availability of genetic testing and familial screening has led to the identification a relevant

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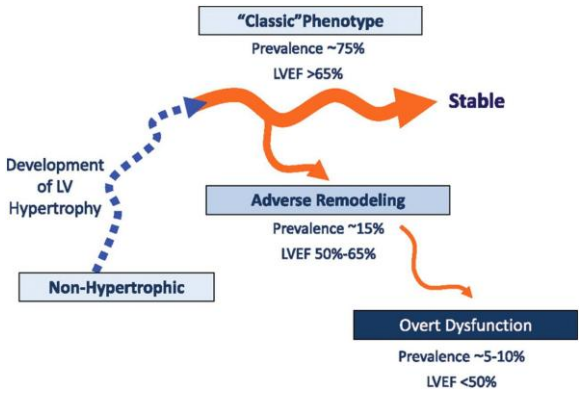

Figure 1 Stages of hypertrophic cardiomyopathy. LVEF, left ventricular ejection fraction.

population of genotype-positive/phenotype-negative individuals, carrying HCM-causing mutations. This represents an opportunity to explore the ultimate frontier in HCM treatment—i.e. preventing the development of the phenotype in predisposed individuals. Notably, heterozygous *MYBPC3* mutation was corrected by CRISPR/Cas9 technology in human pre-implantation embryos using a germline-specific DNA repair response, in which homologous wild-type maternal gene was used as a template. The technique proved to be accurate and a high number of wild-type homozygous embryos were created without off-target effects.[2] This technique will likely never enter clinical practice, as a pre-implant selection of mutation-negative embryos is obviously an easier alternative. However, the study provides an important proof-of-concept stimulating future endeavours.

Since the activation of transforming growth factor-beta (TGF-β)-mediated pathway in animal models of HCM is pivotal in the induction of myocardial hypertrophy and

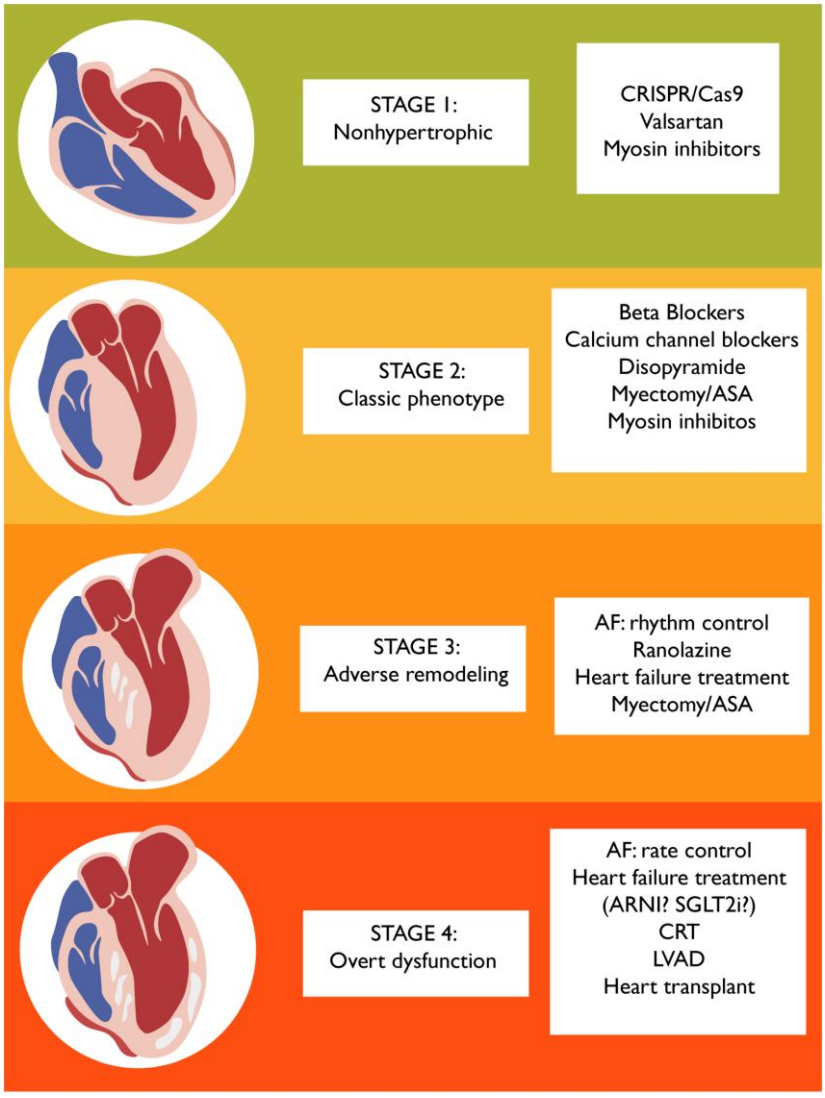

Figure 2 Stage-specific therapy in hypertrophic cardiomyopathy. ASA, alcohol septal ablation; AF, atrial fibrillation; ARNI, angiotensin receptor-neprilysin inhibitor; SGLT2i, sodium-glucose transporter 2 inhibitors; CRT, cardiac resynchronization therapy; LVAD, left ventricular assist device.

fibrosis, the TGF-β inhibitor losartan was administered to young pre-phenotypic HCM transgenic mice, in which it prevented the development of hypertrophy—while no effect was seen in already hypertrophied ventricles.[3] In the subsequent Valsartan for Attenuating Disease Evolution in Early Sarcomeric Hypertrophic Cardiomyopathy (VANISH) trial, valsartan improved cardiac structure and function over 2 years, compared with placebo, in genotype-positive individuals with mild, early HCM phenotype. The study proved challenging and is unavoidably based on small numbers, but ultimately supports the concept that attenuation of disease progression can be achieved in young HCM patients.[4]

In HCM, a multifactorial calcium overload activates calcineurin-mediated pathways, which play a fundamental role in signalling maladaptive hypertrophy. Notably, the calcineurin inhibitor cyclosporin prevented disease manifestation in murine models of HCM overexpressing β-tropomyosin, tropomodulin, and a non-phosphorylable form of myosin light chain. Yet, the well-known side effects of the drug exclude its use as a treatment option in pre-phenotypic patients.[5] Statins, through the inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA), may also impede the activation of several pathways involved in the development of hypertrophy and fibrosis. In young rabbits harbouring the R403Q mutation, atorvastatin blunted the myocardial oxidative stress and prevented the development of an HCM phenotype. Nevertheless, these positive results were not confirmed in short-term human studies.[6]

Finally, the first in class selective allosteric inhibitor of cardiac myosin ATPase mavacamten reduces actin–myosin cross-bridge formation and excess contractility as well as improving myocardial energetics, thus specifically targeting the pathophysiology underlying HCM.[7] Early administration of mavacamten in mice harbouring heterozygous pathogenic mutations in cardiac myosin heavy chain blocked the development of LV hypertrophy, cardiomyocyte disarray, and myocardial fibrosis and mitigated hypertrophic and profibrotic gene expression.[7] However, preventive studies in men with myosin inhibitors are still missing and will be challenging to design in an adequately powered population.

Stage II: classic stable hypertrophic cardiomyopathy

The classic HCM phenotype is characterized by a fully expressed hypertrophic phenotype, in which hypercontractility predominates in the absence of extensive fibrotic replacement. In this stage, the most common cause of symptoms is represented by LV outflow tract obstruction (LVOTO) due systolic anterior motion (SAM) of the mitral valve. Since hypercontractility with a strong adrenergic drive has a pivotal role in the development of LVOTO, drugs with negative inotropic effect such as BB, non-dihydropyridine calcium channel blockers (CCBs) and disopyramide have been the mainstay of treatment for decades.

Beta-blockers are the most frequently used medications in HCM, with a particular predilection for non-vasodilating agents (e.g. atenolol, nadolol, bisoprolol, and metoprolol). At our institution, nadolol is the BB of choice since it is well tolerated, usually requires a single administration and presents an advantageous antiarrhythmic profile, as shown in genetic arrhythmic syndromes such as long QT and catecholaminergic polymorphic ventricular tachycardia. In a recent double-blind, placebo-controlled randomized crossover trial, 29 patients with symptomatic obstructive HCM were treated with metoprolol or placebo for 2 weeks in random order. Treatment with metoprolol was associated with a reduction in rest and exercise-induced LVOT obstruction, improvement of HF symptoms, angina, and quality of life.[8] Invasive investigations did not show improvements in pulmonary capillary wedge pressure increase during exercise; nevertheless, metoprolol reduced the degree of mitral regurgitation, increased LV end-diastolic volume and stroke volume at rest and during exercise.[9] Non-dihydropyridine CCB may be an alternative to BB when ineffective or poorly tolerated.[10] However, in patients with hypotension, dyspnoea at rest and very high resting gradients (e.g. >100 mmHg), CCB should be avoided due to the possible vasodilator effect.

Disopyramide is a Class Ia antiarrhythmic drug which is used preferably as an add-on therapy to BB or CCB for refractory symptoms in obstructive HCM. Disopyramide determines a negative inotropic effect both sarcomere-dependent and -independent, mediated by a multichannel inhibition and improvement of calcium homeostasis. Disopyramide has shown several antiarrhythmic effects on the HCM myocardium *in vitro,* including the suppression of early and delayed afterdepolarizations and the transmural homogenisation of repolarization.[11] Large multicentre registries have confirmed the efficacy and safety of this drug that can be routinely started in the outpatient setting.[12] The most important side effects are QTc interval prolongation, though smaller in HCM patients compared with healthy subjects,[11] and anticholinergic side effects (e.g. dry mouth, constipation, urinary retention, blurred vision) that may limit adherence to therapy.

In patients with refractory symptoms despite optimal medical therapy SRTs should be considered, including surgical myectomy and alcohol septal ablation (ASA). Myectomy is considered the gold standard, preferred in young and adult patients including those with multiple abnormalities requiring correction (markedly elongated mitral leaflets, anomalous papillary muscles, chordal slack, coronary artery bridging). ASA should ideally be reserved to fragile patients with high surgical risk, or when surgical expertise is not available. Although very effective in relieving symptoms associated with obstruction, SRTs do not impact a subsequent progression of the cardiomyopathic process. Moreover, most patients worldwide have limited or even no access to experienced centres with adequate expertise.

Allosteric cardiac myosin inhibitors, including mavacamten and aficamten, have been recently developed to address the hypercontractile phenotype at the core of HCM pathophysiology. In the Phase 3 randomized, double-blind, placebo-controlled trial EXPLORER-HCM, 251 symptomatic patients (NYHA Classes II and III) with LVOTO and exercise-induced gradients ≥50 mmHg were randomized to mavacamten or placebo on top or BB or CCB therapy. At the end of the 30 weeks of treatment twice as many patients on mavacamten improved functional capacity and/or symptoms meeting the primary endpoint of a ≥1.5 mL/kg/min increase in pVO_2 with ≥1 NYHA class improvement or ≥3.0 mL/kg/min increase in pVO_2 with no worsening of NYHA class (37% vs. 17%, $P < 0.01$). All the secondary endpoints were met: the mean difference between treatment

and placebo in the change in post-exercise LVOT gradient was −35.6 mmHg (−43.2 + −28.1), the mean difference in pVO_2 change was 1.4 (0.6–2.1), and more than double patients had ≥1 NYHA class improvement in the treatment arm compared with placebo (65% vs. 31%). Furthermore, marked and sustained reduction in serum levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) and Troponin I, two important predictors of long-term outcome in HCM, was reported. Mavacamten was safe and well tolerated with an adverse event profile comparable with placebo. Five patients on mavacamten had an LV ejection fraction (EF) reduction <50% requiring protocol-driven temporary treatment discontinuation that normalized after wash out, allowing study completion on a lower dose.[13] In the pre-specified subanalysis on quality of life, the change from baseline to 30 weeks in Kansas City Cardiomyopathy Questionnaire-Overall Score (KCCQ-OS) was greater with mavacamten than placebo [mean score 14.9, standard deviation (SD; 15 ± 8) vs. 5.4 (13 ± 7); difference +9.1 95% confidence interval (95% CI, 5.5–12.8); $P < 0.0001$], with similar benefits across all KCCQ subscales, mirroring the results obtained with invasive procedures like transcatheter aortic valve replacement.[14] In an echocardiography substudy, mavacamten not only determined a complete resolution of SAM in 81% of patients (vs. 34%, difference 48.8, $P < 0.01$) but also improved measures of diastolic function including left atrial volume index, lateral E/e', in turn associated with reduction in NT-proBNP.[15] Consistently, the cardiac magnetic resonance (CMR) EXPLORER-HCM substudy showed a positive remodelling of chambers' geometry with a reduction of LV mass index, maximal LV wall thickness and confirmed the reduction of left atrial volume.[16] Recently presented interim data from the long-term extension study mirrored those of the primary trial with substantial and sustained improvement in resting and Valsalva LVOT gradients, LV filling pressures, NT-proBNP, and NYHA class at 84 weeks, confirming a favourable safety profile.

In the EXPLORER-HCM trial, the effects on the primary endpoint were more pronounced in patients without compared with those on BB. In a subgroup analyses, similar improvements were observed in heart-rate-independent measures such as LVOT gradients, NYHA class and NT-proBNP in patients with and without BB. Notably, however, the majority of patients on BB had chronotropic incompetence, affecting heart-rate-dependent measures (pVO_2, peak exercise time, peak METS).[17] In the VALOR-HCM trial (A Study to Evaluate Mavacamten in Adults With Symptomatic Obstructive HCM Who Are Eligible for Septal Reduction Therapy), 112 patients with severe symptoms despite maximal medical therapy (BB/CCB ± disopyramide) were randomized to mavacamten or placebo. The trial met the primary endpoint of SRT candidacy since, after 16 weeks, only 18% of patients on mavacamten vs. 77% on placebo (difference 58.9%, 95% CI 44–74%, $P < 0.01$) were still candidates for or underwent SR therapy.[18]

While mavacamten has been approved by the FDA, aficamten, a second myosin inhibitor is currently being developed for clinical use. The main difference between the two is pharmacokinetic, since aficamten has a shorter half-life and shallower dose–response curve, achieving the steady-state concentration within 2 weeks. This potentially renders up- and down-titration easier compared with mavacamten, which reaches steady-state concentration in 6 weeks.[19]

REDWOOD-HCM is a Phase 2, multicentre, randomized, placebo-controlled, double-blind, dose finding clinical trial of aficamten in patients with symptomatic HCM. Cohorts 1 (5–15 mg) and 2 (10–30 mg) enrolled patients with LVOTO (Resting gradient ≥ 30 or post Valsalva gradient ≥ 50 mmHg) on BB or CCB. Data presented at the HFSA Annual Scientific Meeting showed that aficamten was well tolerated with no treatment emergent adverse events that lead to treatment interruption or discontinuation. Patients on aficamten improved LVOT gradients, NYHA class and NT-proBNP compared with placebo (Cytokinetics Announces Results From REDWOOD-HCM and GALACTIC-HF Presented in Late Breaking Clinical Trial Session at the HFSA Annual Scientific Meeting | Cytokinetics, Inc. (gcs-web.com)). Positive results were also been reported from Cohort 3 that evaluated patients with disopyramide as adjunctive background therapy (https://ir.cytokinetics.com/news-releases/news-release-details/cytokinetics-announces-results-cohort-3-redwood-hcm-presented).

Initial data from REDWOOD-HCM OLE included 38 patients in NYHA Class II/III. Most were on BB and/or CCB and 26% were on disopyramide; mean duration of treatment was 26 ± 12 weeks. Within 2 weeks from initiation patients experienced a rapid and sustained reduction in LVOT gradients that improved with up-titration of the drug through 24 weeks of treatment [resting LVOT-G mean change from baseline (SD) = −32.6 (28) mmHg, $P < 0.0001$ at 12 weeks, −32.8 (32.3) mmHg, $P = 0.0003$ at 24 weeks, Valsalva LVOT-G −42.7 (38.7) mmHg, $P < 0.0001$ at 12 weeks, −51.1 (35.3) mmHg, $P < 0.0001$ at 24 weeks]. At 12 weeks, 72% of patients improved by one NYHA class and 7% improved by two classes; at 24 weeks 61% of patients improved by one class and 17% improved by two classes. Furthermore, patients experienced a 70% and 20% reduction, respectively, in NT-proBNP and Troponin I. The drug was well tolerated and no patients developed LVEF < 50% attributed to study drug (https://ir.cytokinetics.com/news-releases/news-release-details/cytokinetics-announces-data-redwood-hcm-ole-and-galactic-hf). KCCQ-OS and all subdomain scores improved. At 12 and 24 weeks, the change from baseline [mean (SD)] change in KCCQ-OS was 16.5 (16.7) ($P < 0.0001$) and 17.6 (24.7) ($P = 0.0015$). A very large clinical improvement (≥20 points) was reported in 36.4% of patients at Week 12% and 40.0% at Week 24 (https://ir.cytokinetics.com/news-releases/news-release-details/cytokinetics-presents-new-data-redwood-hcm-ole-late-breaking-0). Following these positive results, the Phase 3 randomized, placebo-controlled, double-blind, international multicentre clinical trial SEQUOIA-HCM has been designed and is now recruiting. The study will evaluate aficamten in patients with symptomatic LVOTO on background medical therapy including disopyramide for 24 weeks (https://ir.cytokinetics.com/news-releases/news-release-details/cytokinetics-announces-start-sequoia-hcm-phase-3-clinical-trial).

Stage III: adverse remodelling

Up to 15% of patients develop structural abnormalities on the top of the 'classic' HCM phenotype such as LV fibrosis,

worsening diastolic and systolic function in a low-normal range of EF 50–65%. This phenotype should prompt close clinical surveillance, since an EF between 50% and 60% is associated with substantial presence of late gadolinium enhancement (>12–15% of the LV) on CMR, and may predict progression to overt LV systolic dysfunction.[20]

Replacement fibrosis represents an important although as yet unreached therapeutic target in this subset of patients, since several attempts with anti-fibrotic drugs have been elusive in HCM. Spironolactone over 12 months was evaluated in a randomized, double-blind clinical trial that enrolled 53 patients with HCM. The primary endpoint of reduction of serum markers of collagen synthesis and degradation was not met. Moreover, no effect was observed on progression of fibrosis, functional capacity, HF symptoms, and LV geometry.[21] One-year of treatment with Losartan in 318 patients with HCM randomized to the drug or placebo was not associated with neither significant difference in the change in LV mass between the two groups, nor differences in the appearance/progression of fibrosis evaluated by CMR. Notably the therapy was well tolerated irrespective of the presence of LVOTO.[22]

Replacement fibrosis in HCM is often a late consequence of long-standing microvascular ischaemia. Ranolazine is an anti-anginal medication that inhibits the late phase of the inward sodium (Na^+) current (INaL), which is distinctively enhanced in HCM.[23] An augmented INaL leads to Na^+ overload which eventually facilitates cardiomyocyte diastolic Ca^{2+} overload, increases diastolic tension, impairs myocardial perfusion, and has a proarrhythmic effect.[23] *In vitro*, ranolazine ameliorates diastolic function and depresses the arrhythmic propensity of HCM cardiomyocytes.[23] Based on this rationale, the double-blind, placebo-controlled study to assess the efficacy and safety of ranolazine in symptomatic patients with non-obstructive HCM (RESTYLE-HCM) was performed. Ranolazine did not improve functional capacity evaluated by pVO_2 but was associated with a significant reduction in 24 h ventricular arrhythmic burden.[24] In a recent observational study of 119 patients with both obstructive and non-obstructive HCM, treatment with ranolazine was associated with a significant improvement in angina symptoms and almost 80% of patients became asymptomatic or mildly symptomatic. Ranolazine was safe and well tolerated, and no serious adverse events related to the drug have been reported in a total of 308 patient-years. A minority of patients (20%) interrupted the drug mainly due to mild adverse events (gastrointestinal problems, dizziness/headache) or due to disopyramide necessity. Interestingly four patients, mostly with paediatric onset, severe diastolic dysfunction and repeated ischaemia-related arrhythmic episodes did not experience arrhythmic recurrences after ranolazine initiation.[25] Thus, ranolazine may represent a useful adjunct to standard treatment in HCM patients with chronic angina. However, whether treatment may mitigate the long-term effects of microvascular ischaemia, including development of fibrosis, is unknown.

Finally, mavacamten has shown some promise in symptomatic patients with non-obstructive HCM in the dose-ranging Phase II MAVERICK-HCM trial, including a reduction in NT-proBNP and Troponin I. Nevertheless, only one-third of patients with a more severe phenotype (elevated Troponin I or E/e') improved in terms of NYHA class and pVO_2.[26] More definite answers for symptomatic non-obstructive HCM patients will hopefully originate from the ongoing Phase 3 ODYSSEY-HCM trial HCM (NCT05582395).

Stage IV: overt systolic dysfunction

Overt LV systolic dysfunction (EF < 50%) develops in a challenging subset comprising 5–8% of patients with HCM. The severity of such condition is highlighted by a median time from the recognition of systolic dysfunction to a composite outcome of all-cause death (23%), cardiac transplantation (9%), or LVAD implantation (2%) of only 8 years, although interindividual variability is high. The outcome is particularly unfavourable in patients with multiple pathogenic/likely pathogenic sarcomeric variants, AF and LVEF <35%.[20]

Notably, since HCM is characterized by supernormal systolic function, any value of EF <50% should be regarded as severe dysfunction and optimal guideline-directed medical therapy for HF, including angiotensin receptor-neprilysin inhibitor/angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, BB, mineralocorticoid receptor antagonists, and Sodium-glucose transporter 2 (SGLT2) inhibitors and cardiac resynchronization therapy (CRT) should be considered, even though specific data for this condition are lacking.[10] In a cohort of 118 patients from Tufts HCM Institute with EF < 50%, 48% achieved clinical stability in NYHA Class I/II with HF treatment including selected use of CRT. These therapeutic options appeared to improve the prognosis of this subset of patients compared with historical controls.[27] Nevertheless, the outcome of systolic dysfunction in HCM, when subtended by diffuse replacement fibrosis, is often poor and may not respond well to medical therapy.

Sodium-glucose transporter 2 inhibitors through pleiotropic and still not completely understood effects, have consistently shown a significant reduction in hospitalizations for HF and cardiovascular death in patients with and without Type 2 diabetes mellitus, independent of the underlying condition and LVEF. Since patients with HCM are routinely excluded from large heart failure with preserved ejection fraction trials, no data are currently available about the tolerability and safety of SGLT2 inhibitors in HCM. To fill this gap, the EMPA-REPAIR trial will evaluate the effect on pVO_2 of empagliflozin compared with placebo in patients with HCM (NCT05182658). Likewise, sacubitril-valsartan similarly is under evaluation in a small cohort of patients with HCM as part of the SILICOFCM project.[28]

Cardiac resynchronization therapy, according to the most recent AHA/ACC guidelines, should be considered in symptomatic patients despite optimal medical therapy with LVEF < 50% and left bundle branch block, in order to improve symptoms. Such recommendation, however, is based on very limited and to some extent conflicting data.[10] A recent study showed that only 0.4% of patients ($n = 9$) with EF < 50% and abnormal ventricular conduction received CRT. There was no difference in the rate of adverse events (LVAD implantation, HT, or death) compared with a control cohort of patients matched for age and EF, yet LVEF remained stable during a mean follow-up of 13 ± 8 years.[29]

In patients with refractory HF symptoms, options are largely confined to heart transplant. The small LV cavities,

restrictive pathophysiology and biventricular involvement of advanced HCM often undermine the possibility of LV assist device (LVAD) placement, and patients with HCM have been excluded from clinical trials evaluating the effectiveness of LVAD. Nevertheless, in the previously cited cohort from Tufts, 12 of 61 patients received mechanical circulatory support, of whom 11 underwent a continuous-flow LVAD placement as a bridge to transplant.[10] Candidates for LVAD should be carefully selected among those with an LV end-diastolic diameter >55 mm, without right ventricular dysfunction or restrictive physiology, and without anatomical obstacles to the inflow cannula (LV hypertrophy in the mid and distal LV, LV muscle bundles).[30]

Hypertrophic cardiomyopathy patients with advanced HF represent excellent candidates for heart transplant (HT) and the number listed has almost doubled in the last 20 years with post-operative survival of 92% and 83%, respectively, at 1 and 5 years. Unfortunately, mortality while on list remains high, with minimal decline in recent years.[31] In view of the atypical presentation of refractory HF in HCM, often associated with relatively preserved systolic function, late referral due to underappreciation of disease severity is still too common. This should be avoided by careful follow-up of patients starting from the adverse remodelling stage.

Atrial fibrillation

Atrial fibrillation is the most common arrhythmia in patients with HCM, is associated with high risk of thromboembolic complications, and demands anticoagulation independent of the CHA(2)DS(2)-VASc score. Its prevalence increases proportionally with disease severity, and is almost constant in patients with overt dysfunction. Rhythm control is the preferred strategy in all stages, as AF is often tolerated poorly by HCM patients, and its control plays an important role in preserving haemodynamic compensation and quality of life. Nevertheless, rate control becomes unavoidable in long-standing disease with severe atrial dilatation, when even aggressive strategies involving transcatheter ablation usually fail. Disopyramide may be used as an initial step in rhythm control, associated with a rate controlling agent, due to the potential enhancement of atrioventricular conduction during AF recurrences.[10] Amiodarone is the most effective option, but best avoided in young individuals due to its common long-term toxicity.[32] Transcatheter ablation is most used early after the onset of AF, but often requires multiple procedures and continued use of antiarrhythmic drugs in HCM patients.[32] In patients with AF undergoing myectomy, the Maze procedure with exclusion of the LA appendage has proved safe and effective in the maintenance of sinus rhythm.[32] In patients with refractory AF, rate control with BB and or CCB is generally effective, although an ablate and pace approach may be selectively required in compromised patients.

Sudden cardiac death prevention

Sudden cardiac death in HCM is a rare but devastating event, which may occur in any stage of the disease. Data from the SHaRe registry show that lifetime cumulative incidence of ventricular arrhythmias can be as high as 32% (95% CI 23–40) in patients diagnosed <40 years of age, but only about 1% in those diagnosed >60 years.[33] Prevention of SCD is a primary aim in HCM patients independent of the stage of disease, while phenotype-negative mutation carriers are considered not to be at risk. Arrhythmic prevention is most challenging in stable, asymptomatic or mildly symptomatic patients (Stage 2), because the impact of the device on quality of life is greatest, but so is the potential benefit (due to absence of competing risks). In the more advanced Stages 3 and 4, HF-related outcomes become more prevalent and medicalization is more intense, so that shared decision-making is less difficult but the challenges in appropriate candidates remain.

Two main instruments exist for the prediction of SCD in adult patients: the HCM Risk-SCD and the AHA/ACC guidelines. The HCM Risk-SCD is a prognostic and validated model derived from a retrospective, multicentre longitudinal cohort of 3675 consecutive patients. Age, maximal LV wall thickness, LA diameter, maximal LVOT gradient, family history of SCD, non-sustained ventricular tachycardia (NSVT), and unexplained syncope were associated with the composite outcome of SCD and appropriate ICD shock and included in the model that estimates the risk of SCD in 5 years for an individual patient. In patients with a 5-risk of SCD >6%, an ICD implantation should be considered, while in case of SCD risk <4% it is generally non-indicated, with an intermediate risk zone in which further prognostic markers such as a significant amount of fibrosis at CMR, LVEF <50%, and the presence of apical aneurysm should be taken into account in the context of a shared discussion regarding risks and benefits of the implantation.[34] The AHA/ACC is a more sensitive but less specific, dichotomic approach in which the presence of at least one of the previously described risk factors allows consideration for an ICD. An important clarification is made in the AHA/ACC guidelines regarding NSVT on Holter monitoring that should be considered as important risk markers in paediatric patients and in adults when they are frequent (≥3 runs), long (≥10 beats) and fast (≥200 b.p.m.) since these characteristics are more predictive of SCD.[10] To better understand the impact of the different approaches, the arrhythmic outcome of patients with HCM followed at US and non-US sites have been recently compared in the Share Registry. Notably, there was a two-fold higher ICD utilization in the US sites, with a lower average burden of traditional SCD risk factors and—consistently—lower rates of appropriate ICD interventions compared with non-US sites. Intriguingly, there was no difference in SCD rates in non-ICD recipients between the two groups.[35] In both instances, the majority of ICDs remained inactive, highlighting the need for a more refined stratification of risk in HCM.

Conclusion

Hypertrophic cardiomyopathy is multifaced and changes its profile constantly over time. Each individual at each stage needs a tailored approach meeting the challenge of such complexity. At the eve of a new era in drug development of genetic cardiomyopathies, we must learn to make the most of the available options, as we wait for novel, more definitive treatments for our patients.

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Data availability

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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