Archives of Cardiovascular Disease 115 (2022) 529–537

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Review

Medical treatment of patients with hypertrophic cardiomyopathy: An overview of current and emerging therapy☆

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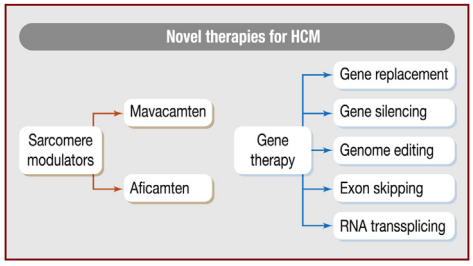
HIGHLIGHTS

- No treatment has produced hypertrophy regression in HCM.
- No treatment has modified the natural history of HCM.
- Treatment of LVOT obstruction includes beta-blockers as first-line agents.
- Treatment of LVOT obstruction includes disopyramide as second-line therapy.
- Sarcomere modulators and gene therapy are under investigation for HCM.
- These new approaches target the pathophysiological basis of HCM.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 27 April 2022
Received in revised form 6 June 2022
Accepted 8 June 2022
Available online 2 September 2022

Keywords:
Hypertrophic cardiomyopathy
Medical therapy
Gene therapy

ABSTRACT

Several treatments have demonstrated safety and effectiveness in the treatment of patients with hypertrophic cardiomyopathy; however, no drug has been shown to modify the natural history of the disease or to decrease maximal wall thickness. Improvement in our knowledge of the physiopathology of the disease has permitted the development of new therapeutical approaches, including sarcomere modulators and gene therapy. A sarcomere modulator – mavacamten – has been shown to improve exercise capacity, left ventricular outflow tract obstruction, New York Heart Association functional class and health status in a phase 3 trial. Gene therapy – although still far from human experimentation – also has promising characteristics that may radically revolutionize the treatment of hypertrophic cardiomyopathy in the future. This therapy is currently approved for the treatment of select haematological malignancies, inherited

☆ Medical treatment of #HCM. This review provides an overview of medical therapies for the management of patients with #HCM, discusses emerging therapeutic approaches and presents future perspectives. *Twitter address: @glimongelli; @MondaEmanuele.*

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https://doi.org/10.1016/j.acvd.2022.06.003

retinal dystrophy and spinal muscular atrophy, and could potentially correct the genetic alterations of the most frequent sarcomeric forms of hypertrophic cardiomyopathy. This review provides an overview of current conventional therapies for the management of patients with hypertrophic cardiomyopathy, discusses emerging therapeutic approaches and presents future perspectives.

1. Abbreviations

AF atrial fibrillation
ATPase adenosine triphosphatase
DNA deoxyribonucleic acid
HCM hypertrophic cardiomyopathy
HOCM hypertrophic obstructive cardiomyopathy
LVOT left ventricular outflow tract
mRNA messenger ribonucleic acid
MYBPC3 gene encoding myosin-binding protein C
MYH7 gene encoding myosin heavy chain beta
NDHP-CCB non-dihydropyridine calcium channel blocker
NOAC non-vitamin K antagonist oral anticoagulant
NO-HCM non-obstructive hypertrophic cardiomyopathy
NT-proBNP N-terminal prohormone of B-type natriuretic peptide
NYHA New York Heart Association
PRKAG2 gene encoding adenosine monophosphate-activated protein kinase subunit gamma 2
RNA ribonucleic acid

2. Background

Hypertrophic cardiomyopathy (HCM) is a myocardial disease characterized by increased left ventricular wall thickness, not solely explained by abnormal loading conditions [1,2]. The prevalence of the disease among young adults was estimated by echocardiography at 1/500 individuals in the CARDIA study in 1995 [3]. However, its prevalence today, based on contemporary diagnostic approaches (i.e. imaging techniques, genetic tests), is considered to be higher [4].

Familial and non-familial forms of HCM are recognized. The former are caused by mutations in sarcomeric genes, mainly inherited as a dominant autosomal trait, and account for 40–60% of HCM cases [5]. The most common genes involved are those encoding myosin heavy chain beta (MYH7) and myosin-binding protein C (MYBPC3), followed by cardiac troponin I (TNNI3), cardiac troponin T (TNNT2), myosin light chain 2 (MYL2), myosin light chain 3 (MYL3) and tropomyosin alpha-1 chain (TPM1). Other less common genetic forms are caused by mutations in genes associated with metabolic or infiltrative disorders, such as alpha-galactosidase (GLA) in Anderson-Fabry disease, transthyretin (TTR) in transthyretin cardiac amyloidosis, lysosome-associated membrane protein 2 (LAMP2) in Danon disease and adenosine monophosphate-activated protein kinase subunit gamma 2 (PRKAG2) in PRKAG2 disease [6–11].

Carriers of pathogenetic mutations of a sarcomeric gene will not necessarily manifest the phenotype, which can develop at any stage of life (particularly in the period of pubertal growth spurt). In addition, phenotypical expression frequently remains subclinical, and does not affect patients' quality of life or prognosis [12]. Nevertheless, some patients can experience angina, dyspnoea, presyncope, syncope or palpitations, and complications such as atrial fibrillation (AF), stroke, severe diastolic dysfunction, systolic dysfunction (end-stage disease) or sudden cardiac death [13–15].

Currently, no treatment has been demonstrated to be effective in producing regression of hypertrophy or modifying the natural history of the disease [16–18]. However, the recent acquisition of further knowledge regarding the genetics and physiopathology of the disease has allowed the development of new pharmacological approaches, such as sarcomere contractility modulators and gene therapy.

In this review, we will discuss conventional and innovative therapeutic strategies to treat patients with hypertrophic obstructive cardiomyopathy (HOCM) and non-obstructive HCM (NO-HCM).

3. Management of left ventricular outflow tract obstruction

The obstructive form of HCM (i.e. HOCM) has been historically defined by the presence of a left ventricular outflow tract (LVOT) peak gradient $\geq$ 30 mmHg [1]. The obstruction significantly affects cardiac haemodynamics only in case of a peak gradient $\geq$ 50 mmHg [1,2]. Severe LVOT obstruction (i.e. $\geq$ 50 mmHg) can be found at rest and/or with exercise in 70% of patients with HOCM [19], and can vary considerably over time. The dynamic nature of LVOT obstruction is mainly influenced by variation in the state of preload, afterload and contractility, and these aspects should be considered in the therapeutic decision-making (i.e. discontinuing or avoiding high doses of diuretics, vasodilators and inotropes that could worsen the gradient).

Non-vasodilating beta-blockers are recognized as the first-line therapy, with the non-dihydropyridine calcium channel blockers (NDHP-CCBs) verapamil and diltiazem considered as possible alternatives (Table 1). In patients with refractory symptoms despite the maximal dosage of such medication, the addition of disopyramide, adequately titrated, is usually considered as the second-line strategy [1,2] (Fig. 1).

Through their negative chronotropic and inotropic effects, beta-blockers prolong the diastole and promote relaxation of hypertrophic myocardium, potentially improving left ventricular filling. Historically, propranolol was the first beta-blocker adopted, but its use was supported by small cohort studies conducted about 50 years ago. More recent options are metoprolol, bisoprolol and nadolol, although the choice of drug is variable, and is frequently based on the experience of the centre and the individual practitioner [20]. The efficacy of nadolol (40–80 mg/day) and bisoprolol (5–10 mg/day) in reducing LVOT obstruction after exercise was assessed prospectively in 27 asymptomatic and mildly symptomatic patients with HOCM (with an LVOT gradient > 50 mmHg after exercise). After 12 ± 4 months, in more than half of patients (52%), the gradient after exercise was < 30 mmHg, and in another third of patients (33%) the gradient reduction was $\geq$ 20 mmHg [21].

Recently, a retrospective study also investigated the effectiveness and safety of bisoprolol in a consecutive cohort of 92 symptomatic adults with HOCM. Overall, 17% of patients reached a primary endpoint of LVOT gradient < 30 mmHg and at least one New York Heart Association (NYHA) class improvement, and 62% achieved an LVOT gradient < 50 mmHg, delaying the need for disopyramide and/or septal reduction therapy [22].

In addition, a recent single-centre randomized double-blind placebo-controlled crossover trial compared the effect of

Table 1
Drugs that have demonstrated effectiveness in the treatment of patients with hypertrophic cardiomyopathy.

	Initial dose	Maximal dose	Side effects
Management of LVOT obstruction			
Beta-blockers			Chronotropic incompetence, hypotension, AV conduction defect, asthma
–Propranolol	40 mg b.i.d.	80 mg t.i.d.	
–Bisoprolol	1.25 o.d.	15 mg o.d.	
–Metoprolol tartrate	25 mg b.i.d.	100 mg b.i.d.	
–Nadolol	40 mg o.d.	80 mg b.i.d.	
NDHP-CCBs			AV conduction defect, ankle oedema
–Verapamil	40 mg b.i.d.	240 mg b.i.d.	
–Diltiazem	60 mg b.i.d.	180 mg b.i.d.	
Antiarrhythmic class IA			
–Disopyramide retard	125 mg b.i.d.	250 mg t.i.d.	Anticholinergic effects, QT prolongation
Management of symptoms in patients with NO-HCM			
Beta-blockers	See above	See above	See above
NDHP-CCBs	See above	See above	See above
Management of AF			
Antiarrhythmic agents			
–Amiodarone	200 mg o.d.	200 mg o.d.	QTc prolongation, photosensitivity, thyroid dysfunction, pulmonary interstitial disease
–Sotalol	40 mg b.i.d.	80 mg t.i.d.	QTc prolongation, asthma, chronotropic incompetence, AV conduction defect
–Disopyramide	See above	See above	See above
Anticoagulant agents			Increased bleeding risk in different organs and tissues, allergic reactions in sensitive individuals
–Warfarin	INR target 2.0–3.0		
–Dabigatran	150 mg b.i.d.		
–Rivaroxaban	20 mg o.d.		
–Apixaban	5 mg b.i.d.		
–Edoxaban	60 mg o.d.		
Sarcomere modulators			
Myosin inhibitors			
–Mavacamten	Not approved yet		
–Aficamten	Not approved yet		

AF: atrial fibrillation; AV: atrioventricular; b.i.d.: bis in die (twice a day); INR: international normalized ratio; LVOT: left ventricular outflow tract; NDHP-CCBs: non-dihydropyridine calcium channel blockers; NO-HCM: non-obstructive hypertrophic cardiomyopathy; o.d.: omni die (once a day); t.i.d.: ter in die (three times a day).

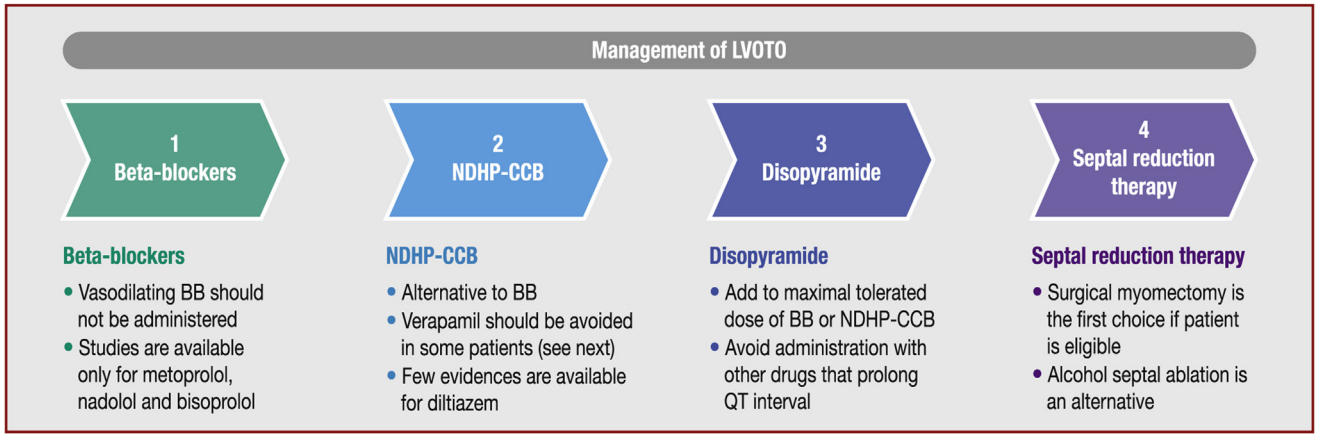

Fig. 1. Management of left ventricular outflow tract obstruction (LVOTO). BB: beta-blockers; NDHP-CCB: non-dihydropyridine calcium channel blockers.

metoprolol and placebo in patients with HOCM. After 2 weeks, metoprolol was superior to placebo in reducing LVOT gradient (at rest, at peak exercise and after exercise), improving symptoms (i.e. NYHA functional class) and ameliorating quality of life (i.e. Kansas City Cardiomyopathy Questionnaire Overall Summary Score [KCCQ-OSS]) [23]. However, despite the significant reduction in LVOT gradient, no significant improvement in exercise capacity was observed with metoprolol, probably related to the heart rate reduction.

In the context of NDHP-CCBs, verapamil can improve left ventricular diastolic filling [24], mainly by reducing temporal asynchrony. Calcium channel block, unfortunately, also extends to the smooth muscle of peripheral vessels, potentially determining a vasodilation that can increase LVOT obstruction. Moreover,

verapamil can cause serious complications, such as sinus arrest, sinus bradycardia, atrioventricular block, postural hypotension and pulmonary oedema, especially if administered to patients who have sinus or atrioventricular node disease, high pulmonary capillary wedge pressures or very high resting gradients (> 100 mmHg) [2,25]. Diltiazem has similar properties to verapamil, but only a few studies are available on its specific effectiveness in patients with HCM.

Disopyramide is an antiarrhythmic agent in class IA of the Vaughan Williams classification. The application of a sodium channel antagonist for the management of LVOT obstruction is based on its negative inotropic effect, which decreases contractility, a key determinant of obstruction. The drug should be administered in addition to beta-blockers to limit cardiac anticholinergic effects that could lead to a rapid ventricular response in patients with AF. The side effects associated with disopyramide include xerostomia, nausea, constipation, urinary retention and QT prolongation. Therefore, diuresis, bowel movement and QT interval should be assessed periodically, and other drugs that prolong the QT interval should be discontinued or avoided. The effectiveness of disopyramide has been demonstrated in a multicentre study, where the drug reduced LVOT gradient at rest and improved NYHA functional class, delaying the need for non-pharmacological intervention in 66% of patients with HOCM [26].

Finally, low doses of diuretics can be given to reduce lung congestion, paying close attention to avoid excessive preload contraction, which can increase LVOT obstruction.

4. Management of symptoms in patients with NO-HCM

About one-third of patients with HCM do not have a gradient ≥ 50 mmHg at rest or during exercise [19]. Pharmacological therapy in patients with NO-HCM is complicated by the absence of clinical trials and the not univocal physiopathology of symptoms (e.g. diastolic dysfunction, myocardial ischaemia, systolic dysfunction) [27–29].

Pharmacological management of symptomatic patients with NO-HCM and preserved ejection fraction includes beta-blockers and NDHP-CCBs as first-line therapy [1,2], and loop/thiazide diuretics and aldosterone antagonists as the second-line strategy to improve symptoms in case of dyspnoea and volume overload (Fig. 2).

According to the patient's co-morbidities [2], lifestyle interventions and specific drugs can be required (e.g. weight loss and aerobic exercise for obesity [30], renin-angiotensin-aldosterone system inhibitors for hypertension, nitrates for angina relief and lipid-lowering and antiplatelet agents for atherosclerotic disease). Moreover, the administration of the angiotensin receptor blocker losartan prevented left ventricular hypertrophy and fibrosis development in mouse models, if administered early in life.

The effect of losartan in patients with HCM has been studied in some randomized controlled trials. The first study, including patients with NO-HCM, assessed the role of the drug in delaying the progression of hypertrophy and fibrosis [31], and concluded that losartan could moderately postpone left ventricular hypertrophy. In the INHERIT trial, losartan failed to demonstrate effectiveness in promoting left ventricular hypertrophy regression on cardiac magnetic resonance imaging in patients with or without LVOT obstruction [32]. In the VANISH trial, valsartan proved to be safe and effective in improving a composite endpoint, including measures of cardiac morphology, function and remodelling, in individuals with sarcomeric HCM-related genotype and no or mild clinical manifestations [33].

Ranolazine, a cardiac late sodium current inhibitor, was tested in a double-blind placebo-controlled pilot study in symptomatic patients with NO-HCM, without demonstrating any improvement in functional capacity [34]. Similar results were obtained in a randomized controlled trial in which trimetazidine, a direct inhibitor of fatty acid β-oxidation, was administered in patients with symptomatic NO-HCM [35]. A trial explored the effect on exercise capacity of eleclazine, a more potent and selective late sodium current inhibitor than ranolazine, but was terminated prematurely because of side effects in a parallel trial in ischaemic heart disease [36].

In patients with end-stage systolic dysfunction, defined by a left ventricular ejection fraction ≤ 50%, treatment should follow the current guidelines on heart failure with reduced ejection fraction, which include renin-angiotensin-aldosterone system inhibitors, angiotensin receptor-neprilysin inhibitors (ARNIs), beta-blockers, mineralocorticoid receptor antagonists (MRAs), sodium-glucose co-transporter-2 (SGLT2) inhibitors and other diuretics, in addition to discontinuation of negative inotropic agents [37]. An implantable cardioverter defibrillator, cardiac resynchronization therapy, mechanical circulatory support and heart transplantation should also be considered, when appropriate [38].

5. Management of AF

AF is the most common arrhythmia in the HCM population, and its onset impacts patients' quality of life and increases thromboembolic risk [39–41]. Only a few data inform the management of AF in patients with HCM, and treatment recommendations are essentially extrapolated from AF guidelines [42] (Fig. 3).

5.1. Anticoagulant drugs

In patients with HCM, the CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥ 75 years [Doubled], diabetes, stroke/transient ischaemic attack/thromboembolism [Doubled] – vascular disease, age 65–74 years and sex category [Female]) does not predict stroke risk; consequently, it should not be applied [43]. Therefore, in the case of AF, anticoagulation should always be considered in HCM, unless contraindicated.

In individuals taking warfarin, time at therapeutic range could be negatively affected by various factors. In addition, recent observational data advocate the use of novel non-vitamin K antagonist oral anticoagulants (NOACs), showing that the two treatments have a similar risk of stroke and major bleeding, but that NOACs are associated with lower all-cause mortality and composite fatal cardiovascular events, supporting the advantageous use of these medications in patients with HCM and AF [44,45].

5.2. Antiarrhythmic drugs

AF onset in patients with HCM contributes to the development of heart failure. Restoring sinus rhythm and preventing AF recurrence is desirable, if possible, and sotalol, disopyramide and amiodarone are the main therapeutic options.

Amiodarone is generally the preferred agent for rhythm control [46–48], although a risk-benefit assessment should precede its prescription, given the adverse reactions associated with its prolonged administration. Sotalol has been shown to significantly improve exercise tolerance and suppress supraventricular and ventricular arrhythmias in patients with HCM [49]. Disopyramide is a possible alternative in patients with LVOT obstruction, although it cannot be administered with amiodarone or sotalol because of the risk of QT prolongation, and its efficacy is not proven [1,2]. Among other antiarrhythmic agents, flecainide and propafenone are not recommended, given their proarrhythmic effect and concerns regarding their safety in ischaemic patients with ventricular arrhythmia [50]. Moreover, although rarely used, dofetilide was well tolerated in

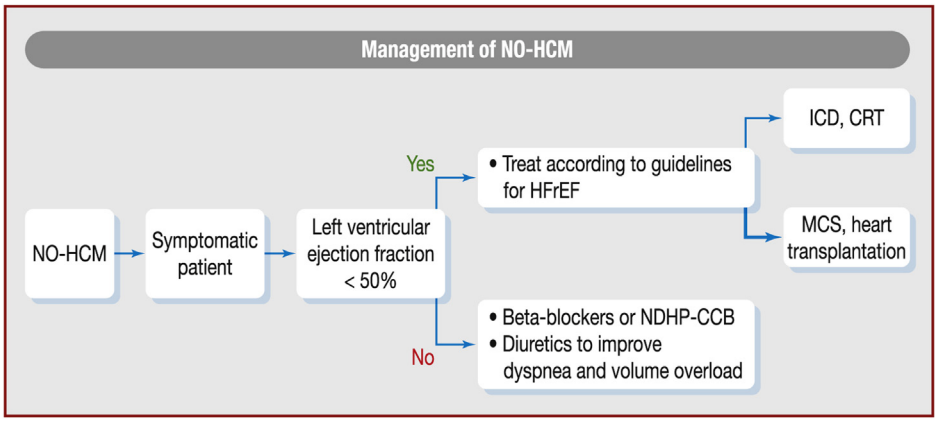

Fig. 2. Management of symptoms in patients with non-obstructive hypertrophic cardiomyopathy (NO-HCM). CRT: cardiac resynchronization therapy; ICD: implantable cardioverter defibrillator; HFrEF: heart failure with reduced ejection fraction; MCS: mechanical circulatory support; NDHP-CCB: non-dihydropyridine calcium channel blockers.

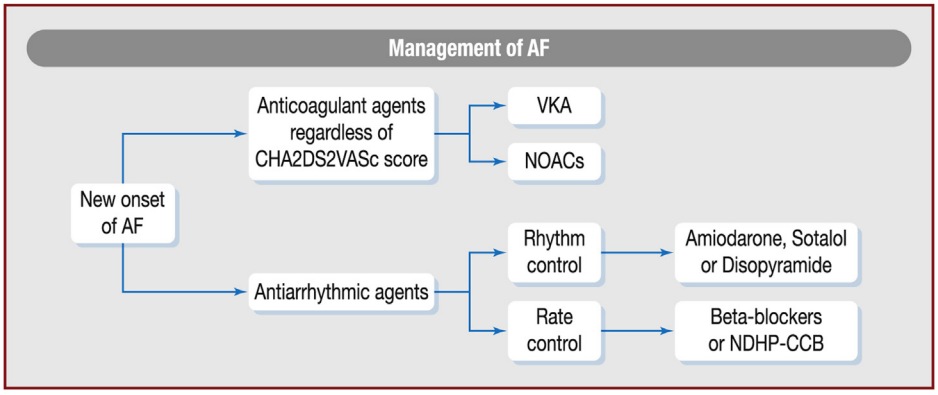

Fig. 3. Management of atrial fibrillation (AF) in patients with hypertrophic cardiomyopathy. CHA_2DS_2-VASc: Congestive heart failure, Hypertension, Age ≥ 75 years (Doubled), Diabetes, Stroke/transient ischaemic attack/thromboembolism (Doubled) – Vascular disease, Age 65–74 years and Sex category (Female); NDHP-CCB: non-dihydropyridine calcium channel blockers; NOACs: non-vitamin K antagonist oral anticoagulants; VKA: vitamin K antagonist.

patients with HCM and AF, and facilitated arrhythmic management in one retrospective case series of 25 patients [51].

In patients who are refractory despite optimal therapy, catheter or surgical ablation could be a resource to improve symptom tolerance and prevent recurrences in recent-onset AF. However, pulmonary vein isolation, despite positive results at short- and mid-term follow-up, does not have satisfactory effects in the long term, and a second procedure is required in about 50% of patients [52].

Finally, if rhythm control is not feasible or achievable, rate control can be obtained with beta-blockers (metoprolol, nadolol, bisoprolol) or, if left ventricular ejection fraction is preserved, with NDHP-CCBs (verapamil and diltiazem). In the absence of LVOT obstruction, patients with end-stage HCM and AF with rapid ventricular response can be treated with digoxin. The last resource to be considered in patients in whom pharmacological rate control is unfeasible is atrioventricular node ablation with ventricular pacing.

6. Novel agents

Since HCM was described in 1957, by a series of eight autopsies revealing the presence of asymmetrical hypertrophy of the heart, 65 years have passed, and many efforts have been made to understand the physiopathology and improve medical therapy. Current research is active in developing disease-modifying drugs capable of preventing or regressing left ventricular hypertrophy.

6.1. Sarcomere modulators

In the normal heart, myosin shifts in equilibrium between two different forms: an open-headed structure; and a super-relaxed state. The first form is characterized by high adenosine triphosphatase (ATPase) activity, available for actin cross-bridge formation, whereas the second form shows low ATPase activity, not available for interaction with actin. The maintenance of the super-relaxed state of a significant proportion of myosins is essential to maintain contractile and energetic homeostasis, representing an evolutionary conserved energy-saving mechanism.

A recent hypothesis suggests that in the sarcomeric form of HCM, the main determinant of the disease is the absence of inhibition of myosin ATPase activity caused by the missing binding between myosin-binding protein C and myosin mesa, a portion of the myosin catalytic domain with regulatory properties [53]. Disease-causing mutations in sarcomeric genes are responsible for a reduction in the inhibition of myosin ATPase, resulting in an increase in the number of open-headed myosins, leading to an hypercontractility state, responsible for increased energy cost of force generation. This phenomenon is considered to be the main driver of HCM pathophysiology.

Thus, myosin ATPase could be considered a new specific pharmacological target, and negative allosteric modulators of cardiac-specific myosin are a promising pathophysiological-based treatment for HCM (Fig. 4).

In preclinical phases, mavacamten (MYK-461) administration to murine models of HCM has demonstrated effectiveness in

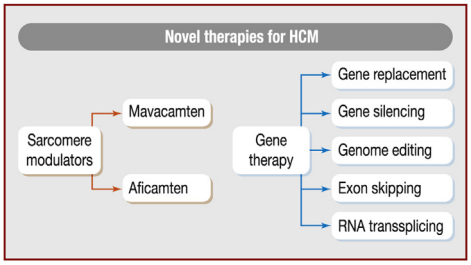

Fig. 4. Central Illustration. Novel therapies for the management of hypertrophic cardiomyopathy (HCM). RNA: ribonucleic acid.

attenuating the development of hypertrophy, and promoting its regression if already manifested [54]. Subsequently, PIONEER-HCM, a phase 2 open-label pilot study involving 21 symptomatic patients with HOCM, demonstrated significative improvements in LVOT gradients after exercise, symptoms and peak oxygen consumption [55]. Moreover, another phase 2 clinical trial, MAVERICK-HCM, proved the safety and tolerability of mavacamten in 59 subjects with symptomatic NO-HCM. In this case, treatment was associated with a significant reduction in cardiac biochemical variables, N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) and cardiac troponin I [56].

In a second stage, the multicentre randomized double-blind placebo-controlled phase 3 EXPLORER-HCM trial studied mavacamten effectiveness in 251 individuals with symptomatic HOCM on standard medical treatment (except for disopyramide), with promising results [57]. Patients with HOCM (with an LVOT gradient $\geq$ 50 mmHg) and NYHA class II–III symptoms were assigned to receive mavacamten or placebo. A significant proportion of patients on mavacamten (37%) met the primary endpoint ($\geq$ 1.5 mL/kg per minute increase in peak oxygen consumption and at least one NYHA class reduction, or $\geq$ 3.0 mL/kg per minute increase in peak oxygen consumption without NYHA class worsening) compared with 22% on placebo. In addition, patients on mavacamten showed a greater reduction in LVOT gradient after exercise and greater increases in peak oxygen consumption and symptom improvement compared with those on placebo.

Secondary analysis from EXPLORER-HCM showed that after 30 weeks of therapy, in the treated group, compared with placebo, significative improvements in several echocardiographic features, particularly left atrial volume index, interventricular septal thickness and E/e' septal and lateral ratio, were detected [58]. Blunted peak LVOT gradient at rest, following the Valsalva manoeuvre and after exercise, was achieved with only a 4% reduction in left ventricular ejection fraction, and without alteration of the chronotropic profile. Moreover, among patients with mitral systolic anterior motion at baseline, the difference in systolic anterior motion resolution between the experimental and placebo arms was 46.8% (95% confidence interval 34.5–59.2%; $P < 0.0001$). Improvement in left atrial volume index was identified as a significant predictor of a decrease in high-sensitivity cardiac troponin I and NT-proBNP, and an increase in exercise capacity, consistent with previous observations [59].

Based on the ground-breaking phase 3 EXPLORER-HCM trial, the United States Food and Drug Administration approved Camzyos™ (mavacamten 2.5 mg, 5 mg, 10 mg and 15 mg capsules; Bristol Myers Squibb, New York, NY, USA) for the treatment of adults with HOCM and NYHA class II–III.

Recently, the results of the VALOR-HCM trial (A Phase 3 Study to Evaluate Mavacamten in Adults With Symptomatic Obstructive HCM Who Are Eligible for Septal Reduction Therapy) were presented. The purpose of this trial was to evaluate the ability of treatment with mavacamten to reduce the number of septal reduction therapies in subjects on maximally tolerated medical therapy and considered eligible, in accordance with the current guidelines [60]. The results of the trial indicated that mavacamten significantly reduced eligibility for needing septal reduction therapy among symptomatic patients with HOCM. In detail, the primary endpoint (decision to proceed with septal reduction therapy or guideline eligible at week 16) for mavacamten versus placebo was 17.9% vs 76.8%, respectively ($P < 0.0001$).

Potential inconveniences of mavacamten treatment are the 6-week period required to reach steady state concentration, and the induction of cytochrome P450 3A4 (CYP3A4) and 2B6 (CYP2B6) in in vitro studies – a potential trigger for pharmacological interactions.

Aficamten (CK-274) is a novel cardiac myosin inhibitor with a human half-life adequate for single daily administration, achieving steady state within 2 weeks, and with no evidence of cytochrome P450 induction or inhibition in preclinical investigations [61]. For these properties, aficamten is considered a manageable sarcomere modulator, and the effect of different doses in patients with HOCM was studied in REDWOOD-HCM (Randomized Evaluation of Dosing With CK-274 in Obstructive Outflow Disease in HCM), a phase 2 trial. REDWOOD-HCM was a double-blind dose-finding trial that randomized symptomatic patients with HOCM to aficamten 5 mg titrated up to 15 mg (cohort 1), aficamten 10 mg titrated to 30 mg (cohort 2) or placebo. The primary endpoint was to evaluate the safety and tolerability of aficamten. After 10 weeks of treatment, both treatment cohorts showed significant reductions LVOT gradient at rest and after the Valsalva manoeuvre, and this reduction was dose dependent. Treatment with aficamten was well tolerated, with similar occurrences of adverse events in patients on aficamten or placebo.

7. Gene therapy

Gene therapy is a fascinating treatment that theoretically acts on the pathophysiological substrate of hypertrophy, preventing phenotype manifestation if administered in the early preclinical phases of the disease (Fig. 4). In 40-60% of patients with HCM, a pathogenetic mutation can be detected, and MYH7 and MYBPC3 are the genes most frequently involved [5,62–64].

Gene therapy is based on the introduction of genetic material into target cells through lipid or viral vectors. After initial issues about the efficacy and safety of gene delivery vectors, in the 2000s, some early-phase trials demonstrated the beneficial effect of transduction of autologous haematopoietic stem cells in different subsets of patients. These studies laid the basis for the approval by the United States Food and Drug Administration in 2017 of therapy involving chimeric antigen receptor (CAR) T cells [65] and gene replacement in retinal pigment epithelium-specific 65 (RPE65)-mediated inherited retinal dystrophy [66] and in spinal muscular atrophy type 1 (SMA1) [67,68]. Therefore, there has been significant progress in the treatment of inherited diseases, that has permitted the development of cardiac genes based on the tropism of certain serotypes of adeno-associated virus (AAV) for the heart. The approaches under investigation for HCM treatment include gene replacement therapy, gene silencing, genome editing, exon skipping and ribonucleic acid (RNA) trans-splicing (Table 2).

Gene replacement therapy is the ideal technique for non-sense mutation, permitting insertion of the wild-type complementary deoxyribonucleic acid (DNA) of the defective gene in the nucleus where the complementary DNA is transcribed and, subsequently, the exogenous messenger RNA (mRNA) is translated into a functional protein that can remedy the insufficiency of the mutated endogen protein. Gene replacement therapy is particularly promising for MYBPC3 mutations, often characterized by a deficiency in

Table 2
Genetic techniques with a potential application in treatment of patients with hypertrophic cardiomyopathy.

	Description	Evidence
Gene replacement	The wild-type complementary DNA of a defective gene is introduced into the nucleus, where is transcribed and, subsequently, the exogenous mRNA is translated into the functional protein that remedies the insufficiency of the mutated endogen protein	Gene replacement therapy delays hypertrophic changes in a homozygous MYBPC3-targeted knock-in murine model of human neonatal HCM [62]; human induced pluripotent stem cell-derived cardiomyocytes from a patient with HCM carrying a MYBPC3 heterozygous mutation were subjected to trans-splicing and gene replacement treatment, with promising results for gene replacement therapy [71]
Gene silencing	Small molecules of RNA are introduced in the nucleus, where, interacting with endogenous complex, they mediate cleavage of the complementary pathological mRNA, preventing translation of the mutant protein	Silencing the mutant MYH6 allele prevented hypertrophy and diastolic dysfunction in mice [65]
Genome editing	CRISPR/Cas9, a nuclease complex, is transduced in the nucleus, where, breaking a target double-stranded DNA, it permits endogenous mechanisms of DNA repair to correct the mutant allele	Introduction of genome editing constructs into human embryos resulted in activation of a germline-specific DNA repair mechanism with higher efficiency than homology-directed repair [68]
Exon skipping	Antisense oligonucleotides are employed to bind exon splicing enhancers and mask them from trans-acting proteins, resulting in exon skipping of a gene of interest; therefore, the shorter mature mRNA does not contain the mutant exon, and can be translated into a defective protein product that could be still functional	An MYBPC3-targeted knock-in mouse model of HCM was treated with viral-mediated antisense oligonucleotide transduction, preventing hypertrophy and systolic dysfunction, although transitorily [69]
RNA trans-splicing	Therapeutic pre-trans-splicing transcript repairs endogenous mRNA through hybridization with target mutant pre-mRNA during mRNA maturation	Human induced pluripotent stem cell-derived cardiomyocytes from a patient with HCM carrying an MYBPC3 heterozygous mutation were subjected to trans-splicing and gene replacement treatment with the confirmation of trans-splicing feasibility [71]

Cas9: CRISPR-associated protein 9; CRISPR: clustered regularly interspaced short palindromic repeats; DNA: deoxyribonucleic acid; HCM: hypertrophic cardiomyopathy; mRNA: messenger RNA; MYBPC3: gene encoding myosin-binding protein C; MYH6: gene encoding myosin heavy chain 6; RNA: ribonucleic acid.

the protein product, and one study has already demonstrated the effectiveness of gene replacement therapy to delay hypertrophic changes in a homozygous MYBPC3-targeted knock-in murine model of human neonatal HCM [69].

An example of a possible effective gene therapy for HCM is represented by TN-201. Preclinical data on treatment in a severe MYBPC3 mutant mouse model of HCM with TN-201 demonstrated significant and durable disease reversal after a single dose. Given these preliminary results, a natural history study focused on improving our understanding of disease progression and unmet need in carriers of MYBPC3 genetic variants was initiated, and is still ongoing.

The genetic substrate of HCM is heterogeneous, and some patients may have missense mutations, producing structurally anomalous proteins that perturb normal sarcomere function, and could benefit from silencing of mutant alleles. This assumption provides the basis for the application of post-transcriptional RNA interference, a gene silencing process in which small molecules of RNA (siRNA), interacting with an endogenous complex (AGO2-RISC), mediate cleavage of specific complementary mRNA sequences [70], preventing their translation. This therapeutic approach has already been studied in mice, silencing the mutant MYH6 allele, structurally similar to the MYH7 one, with interesting results in the prevention of hypertrophy and diastolic dysfunction [71], demonstrating the potential application in humans.

Another technique, genome editing, could potentially determine correction of the pathogenic genotypes underlying several forms of HCM [72]. The technique employs CRISPR/Cas9, a nuclease complex that breaks a target double-stranded DNA and permits endogenous mechanisms of DNA repair, homology-directed repair and non-homologous end-joining to correct the mutant allele. Genome editing application is limited by the low efficiency of homology-directed repair that is the desired process at the moment, which, unlike non-homologous end-joining, has a low risk of inducing additional mutations [73]. Recently, one study has demonstrated that the introduction of genome editing constructs into human embryos results in the activation of a germline-specific DNA repair mechanism, unknown before, with higher efficiency than homology-directed repair [73], leaving, however, many points of criticism about genome editing.

In a different approach, complementary antisense oligonucleotides are employed to bind exon splicing enhancers and mask them from trans-acting proteins, resulting in exon skipping of a gene of interest. Therefore, the shorter mature mRNA does not contain the mutant exon, and can be translated into a defective protein product that could be still functional. This manipulation of splicing is already approved for the treatment of patients with Duchenne muscular dystrophy [74], and data regarding the potential application of this technique in HCM include a study in which a MYBPC3-targeted knock-in mouse model of HCM was treated with viral-mediated antisense oligonucleotide transduction, with interesting results in terms of preventing hypertrophy and systolic dysfunction, although transitorily [75].

The last type of gene therapy, trans-splicing, repairs endogenous mRNA through hybridization of target mutant pre-mRNA with a therapeutic pre-trans-splicing transcript during mRNA maturation. The feasibility of repair of MYBPC3 mRNA by 5′-trans-splicing in a murine model of HCM was reported in one study – the first evidence of successful 5′-trans-splicing *in vivo* [76]. In another study, human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) from a patient with HCM carrying an MYBPC3 heterozygous mutation were subjected to trans-splicing and gene replacement treatment, with confirmation of trans-splicing feasibility and promising results for gene replacement therapy [77].

8. Conclusions

HCM is a relatively common cardiac disease with frequent familial inheritance as an autosomal dominant trait. Disease impact on life quality and expectancy, if early diagnosis and treatment are achieved, is favourable in most cases, with a minority of patients experiencing heart failure, stroke and sudden cardiac death. As no strategies are available to achieve prevention or reversal of hypertrophy, contemporary research focuses on acquiring additional

knowledge about classical treatments and developing novel therapeutic strategies, such as sarcomere modulators and gene therapy, to modify the disease course. Novel treatments are under development, and could achieve the main purpose of HCM treatment, i.e. preventing (or delaying) the onset of the disease in pathogenic mutation carriers or, otherwise, regressing (or stabilizing) the phenotype in hypertrophic patients.

Sources of funding

The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Disclosure of interest

The authors declare that they have no competing interest.

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