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REVIEW

Pharmacological treatment of hypertrophic cardiomyopathy: current practice and novel perspectives

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Hypertrophic cardiomyopathy (HCM) is entering a phase of intense translational research that holds promise for major advances in disease-specific pharmacological therapy. For over 50 years, however, HCM has largely remained an orphan disease, and patients are still treated with old drugs developed for other conditions. While judicious use of the available armamentarium may control the clinical manifestations of HCM in most patients, specific experience is required in challenging situations, including deciding when not to treat. The present review revisits the time-honoured therapies available for HCM, in a practical perspective reflecting real-world scenarios. Specific agents are presented with doses, titration strategies, pros and cons. Peculiar HCM dilemmas such as treatment of dynamic outflow obstruction, heart failure caused by end-stage progression and prevention of atrial fibrillation and ventricular arrhythmias are assessed. In the near future, the field of HCM drug therapy will rapidly expand, based on ongoing efforts. Approaches such as myocardial metabolic modulation, late sodium current inhibition and allosteric myosin inhibition have moved from pre-clinical to clinical research, and reflect a surge of scientific as well as economic interest by academia and industry alike. These exciting developments, and their implications for future research, are discussed.

Keywords Hypertrophic cardiomyopathy • Left ventricular outflow tract obstruction • Sudden cardiac death • Pharmacological treatment • Beta-blockers • Amiodarone • Ranolazine

Introduction

Hypertrophic cardiomyopathy (HCM) is the most common genetic heart disease, characterized by complex pathophysiology, heterogeneous morphology, and variable clinical manifestations over time.[1–4] Initially perceived as a rare and malignant disease, the spectrum of HCM has subsequently expanded, as new concepts have emerged regarding its true prevalence and clinical profile.[3,5] The disease is known to range from the severe manifestations of early descriptions, to the absence of clinical and morphologic expression, including lack of left ventricular (LV) hypertrophy, in genotype-positive individuals.[6,7] To date, none of the available pharmacological agents have been shown to modify disease development or outcome in HCM patients,[8,9] with the possible exception of diltiazem in preventing LV remodelling.[10] The only interventions believed to have an impact on long-term prognosis are surgical myectomy and the implantable cardiac defibrillator (ICD).[8] Nevertheless, pharmacological therapy plays a very important role in restoring quality of life and reducing the risk of disease-related complications. The main goals of pharmacological therapy in HCM include control of symptoms and exercise limitation, abolition or reduction of dynamic intraventricular gradients, treatment of LV dysfunction and heart failure (HF), control of atrial fibrillation (AF) and ventricular arrhythmias, and prevention of cardioembolism.

After more than 50 years from the first reported case of HCM, only about 2000 patients have been randomized in clinical trials evaluating the efficacy of drug treatments for HCM.[8] Therefore, international guidelines are largely based on the opinion of experts[11,12] and the scientific community is still waiting for robust

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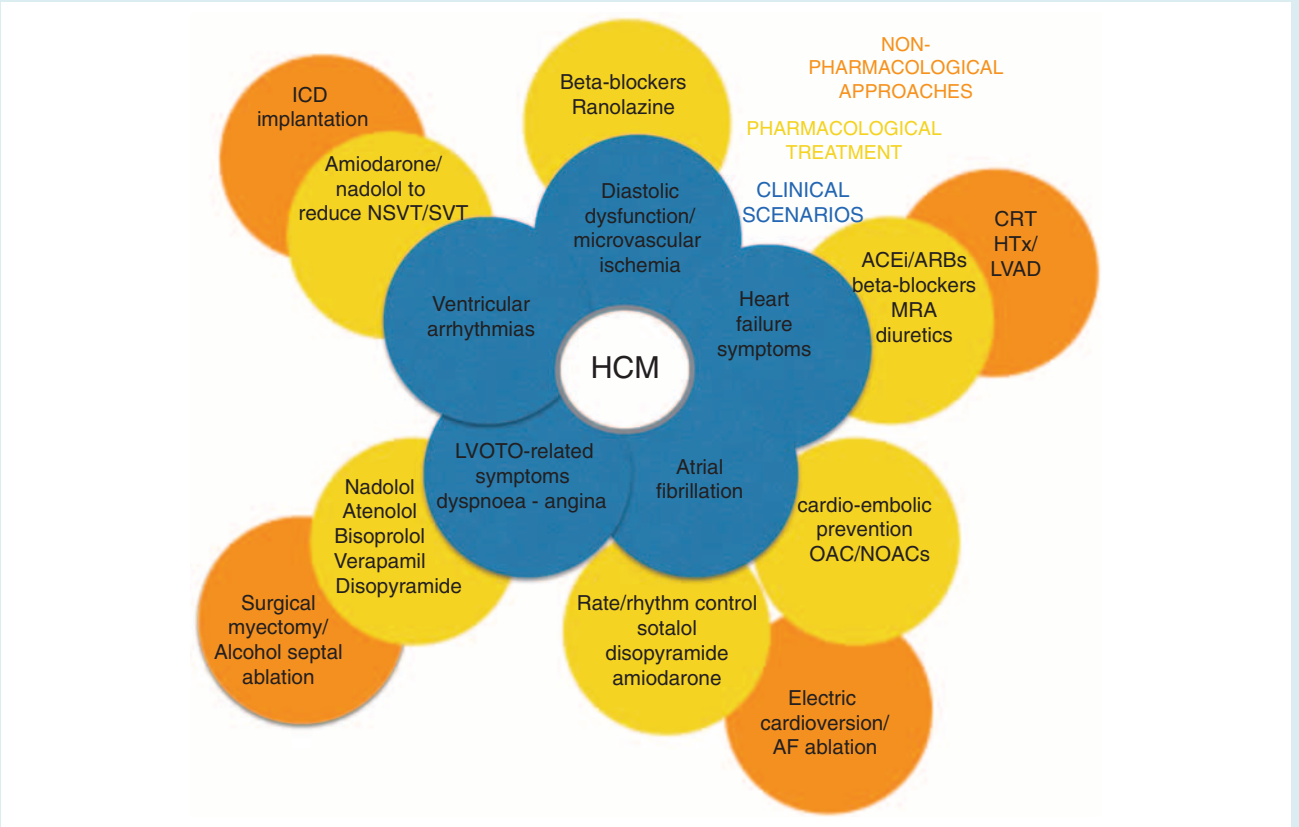

Figure 1 Clinical scenarios and symptoms associated with hypertrophic cardiomyopathy (HCM) and representation of current pharmacological (yellow balloons) and non-pharmacological treatments (orange balloons). ACEi, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARBs, angiotensin receptor blockers; CRT, cardiac resynchronization therapy; HTx, heart transplantation; ICD, implantable cardioverter defibrillator; LVAD, left ventricular assist device; LVOTO, left ventricular outflow tract obstruction; MRAs, mineralocorticoid receptor antagonists; NOACs, novel oral anticoagulants; NSVT, non-sustained ventricular tachycardia; OAC, oral anticoagulation; SVT, sustained ventricular tachycardia.

evidence and disease-specific treatment options. In this paper, we will review the indications of individual agents in the management of HCM in the context of its complex pathophysiology, provide practical therapeutic considerations in the light of the 2014 European Society of Cardiology (ESC) guidelines,[11] and address promising new approaches currently under scrutiny.

Clinical profiles and genesis of symptoms

Hypertrophic cardiomyopathy may be associated with a normal life expectancy and a very stable clinical course. About a third of patients develop HF, related to dynamic LV outflow tract obstruction (LVOTO). In addition, 5–15% show progression to either the restrictive or the dilated hypokinetic evolution of HCM, both of which may require evaluation for cardiac transplantation.[13,14] Patients with HCM can remain asymptomatic for their entire lifetime.[11–13,15] However, symptoms are common (*Figure 1*) and often insidious: for example, reduced exercise tolerance may not be subjectively perceived as abnormal when present from a very young age. Furthermore, quality of life may be subtly but significantly impaired by psychological issues, iatrogenic symptoms, and lifestyle restrictions.[11]

Dyspnoea is common, and reflects high LV filling pressure, diastolic dysfunction or afterload mismatch with mitral regurgitation secondary to LVOTO.[11,15] In addition, paroxysmal AF has been associated with impaired cardiac reserve, defined as reduced exercise capacity and maximal oxygen consumption.[16,17] In patients with LVOTO, symptoms are typically variable over time, exacerbated by dehydration, meals, alcohol, use of vasodilators, and squatting. Less frequently, patients report nocturnal orthopnoea, either the consequence of congestive HF or bradyarrhythmias (AF with slow ventricular response or sinoatrial dysfunction).

Angina affects about 30% of symptomatic adults and is often atypical, occurring at rest and/or postprandially.[18] Angina is typically related to microvascular dysfunction and increased LV wall stress caused by LVOTO, in the absence of epicardial coronary lesions. When typical, angina should prompt specific investigations to exclude myocardial bridging of the left anterior descending artery in children and atherosclerotic coronary artery disease in older patients.

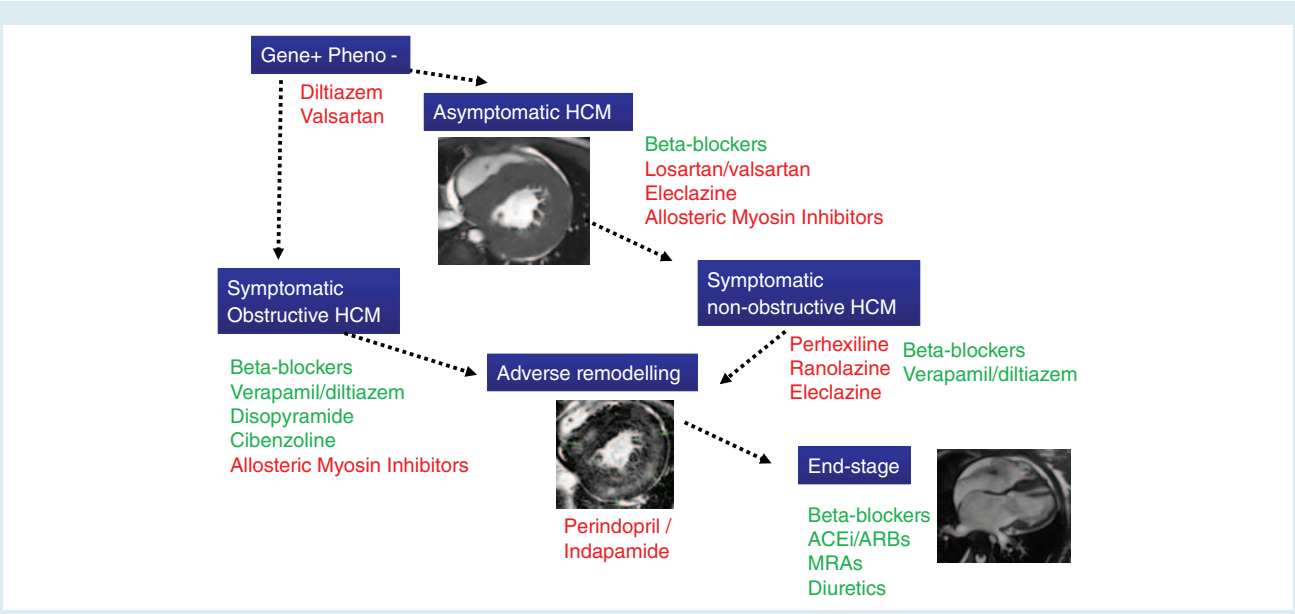

Figure 2 Stages of hypertrophic cardiomyopathy (HCM) and relevant medical treatments. Hatched black arrows reflect potential transitions from one stage to another. Approved medical interventions in specific stage of disease are in green. Drugs under investigation are in red. Pheno, phenotype; ACEi, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; MRAs, mineralocorticoid receptor antagonists.

Pre-syncope or syncope has been reported in about 15–20%, and is generally attributed to sustained ventricular arrhythmias or severe LVOTO, particular when associated with hypovolaemia or occurring during or after effort.[19] However, neurally mediated syncope is common and should be excluded given its radically different prognostic value.[20] Bradyarrhythmias caused by sinoatrial or atrioventricular (AV) block are more common than generally perceived, and may cause syncope even in very young HCM patients.[21] Finally, in a small minority of patients, sudden cardiac death (SCD) may represent the first manifestation of disease.[22,23]

Treatment of dynamic left ventricular outflow tract obstruction

Left ventricular outflow tract obstruction is a complex pathophysiological hallmark of HCM, caused by systolic anterior movement of anomalous mitral valve leaflets, contacting the septum at the subaortic level; less frequently, dynamic gradients may occur at the mid-ventricular level. Classically, LVOTO is defined by peak gradients exceeding 30 mmHg at rest or 50 mmHg during exercise, and is associated with unfavourable prognosis because of HF-related complications.[24] Moreover, a significant association with SCD has been reported.[24,25] In the presence of severe, drug-refractory symptoms, LVOTO represents an indication for surgical myectomy or percutaneous alcohol septal ablation[26] [Class I, level of evidence (LOE) B in the 2014 ESC guidelines).[11] However, pharmacological treatment represents the first approach to all obstructive patients and, if properly used, may be effective in controlling gradients and symptoms for years (*Figure 2*).

Beta-blockers are the most popular and effective agents employed.[11] The classic studies by Braunwald[27] on propranolol date back to the 1960s, showing impressive gradient and symptom reduction in the acute setting.[8,28] Presently, atenolol (50–150 mg/day), nadolol (40–160 mg/day), bisoprolol (5–15 mg/day), and metoprolol (100–200 mg/day) are more frequently used (*Tables 1* and *2*). High doses may be required, and are usually well tolerated. However, side effects (mostly fatigue) should be carefully investigated in order to assess optimal individual dose. At our institutions, nadolol is the drug of first choice, in consideration of its good tolerability, favourable electrophysiological profile, and potent effect of gradient and effective 24-h coverage.[29] In our experience, titrating classic HCM therapy with beta-blockers for dynamic obstruction is relatively easier compared with patients with HF. Obstructive HCM is by definition hyperdynamic and characterized by strong adrenergic drive. A reasonable approach is to start with a quarter of a full dose of beta-blockers (e.g. nadolol 20 mg once daily, atenolol 25 mg once daily, metoprolol 25 mg twice daily, or bisoprolol 2.5 mg once daily) and increase by the same amount every 1–2 weeks to the maximum tolerated dose (usually 80 mg for nadolol and 100 mg for atenolol, 100 mg twice daily for metoprolol, and 10 mg twice daily for bisoprolol, see *Table 1*). Beta-blockers may be titrated based on symptoms, heart rate response, and blood pressure. Non-dihydropyridine calcium channel blockers such as verapamil and diltiazem are considered less effective,[11] although they can be used in patients who are intolerant or have contraindications to beta-blockers.

Table 1 Commonly used drugs for hypertrophic cardiomyopathy (HCM) in adults

Drug	Indication	Starting dose	Maximum dose	Notes	Side effects
Beta-blockers					
Propranolol	Reduction of angina and dyspnoea in patients with or without LVOTO; control of ventricular response in patients with AF; control of ventricular ectopic beats	40 mg bid	80 mg tid	Short half life Drug of choice in newborns/infants	Depression Chronotropic incompetence Decrease in AV conduction Asthma
Atenolol	Same as propranolol	25 mg qd	150 mg qd	Drug of choice in HCM + hypertension	Hypotension Chronotropic incompetence Asthma
Nadolol	Same as propranolol. Reduction in the incidence of NSVT, and SCD prevention, especially when associated with amiodarone	40 mg qd	80 mg bid	Effective for control of obstruction When used qd helps patient compliance	Chronotropic incompetence Decrease in AV conduction Asthma
Metoprolol	Same as propranolol	50 mg qd	100 mg bid	Short half life Usually not useful in HOCM	Chronotropic incompetence Asthma
Bisoprolol	Treatment of systolic dysfunction and HF in end-stage patients	1.25 mg qd	15 mg qd	Usually not useful in HOCM	Chronotropic incompetence Asthma
Calcium channel blockers					
Verapamil	HR reduction; control of ventricular rate in patients with AF Possible enhancement of diastolic filling	40 mg bid	240 mg bid		AV conduction decrease Ankle oedema
Diltiazem	Same as verapamil	60 mg bid	180 mg bid		AV conduction decrease Ankle oedema
Felodipine	Refractory angina in HCM	5 mg qd		Useful in severe microvascular dysfunction	Ankle oedema
Antiarrhythmic agents					
Disopyramide	Relief of dynamic obstruction, in association with beta-blockers	125 mg bid	250 mg tid		QTc prolongation Anticholinergic effects
Amiodarone	AF prevention, control of SVT/NSVT/ventricular ectopic beats, reduction of appropriate ICD interventions	200 mg qd	200 mg qd	Incomplete efficacy for SCD prevention despite reduction of NSVT	QTc prolongation Photosensitivity Thyroid dysfunction Pulmonary interstitial disease
Sotalol	AF prevention	40 mg bid	80 mg tid		
Oral anticoagulants					
Vitamin K inhibitors	Prevention of embolism and ischaemic stroke in patients with paroxysmal or permanent AF	INR target of 2–3 for warfarin and acenocoumarol		Useful after first episode of PAF and/or when LA is enlarged and end stage HF	
Direct thrombin and direct activated factor X inhibitors	Prevention of embolism and ischaemic stroke in patients with paroxysmal or permanent AF	Recommended regimen doses based on individual molecule and patient characteristics		Lack of evidence of efficacy; guidelines suggest vitamin K inhibitors as first choice	

AF, atrial fibrillation; AV, atrioventricular; HF, heart failure; HR, heart rate; HOCM, hypertrophic obstructive cardiomyopathy; ICD, implantable cardioverter defibrillator; INR, international normalized ratio; LA, left atrium; LVOTO, left ventricular outflow tract obstruction; PAF, paroxysmal atrial fibrillation; NSVT, non-sustained ventricular tachycardia; qd, once a day; SCD, sudden cardiac death; SVT, sustained ventricular tachycardia.

Table 2 Pharmacological indications to treat symptoms associated with hypertrophic cardiomyopathy (HCM) based on the 2014 European Society of Cardiology (ESC) and 2011 American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines

Clinical conditions associated with HCM	ESC (2014)	ACCF/AHA (2011)
Dynamic left ventricular outflow tract obstruction		
Beta-blockers	I B	I B
Verapamil/diltiazem (if beta-blockers contraindicated or not tolerated)	I B IIa C (diltiazem)	I B IIb C (diltiazem)
Disopyramide (in association with beta-blockers/verapamil)	I B (IIb C if alone)	IIa B
Oral diuretics (congestive symptoms despite the use of beta-blocker and/or verapamil)	IIb C	IIb C
Dyspnoea and angina in non-obstructive forms and progressive disease		
Beta-blockers	IIa C	I B
Verapamil/diltiazem (if beta-blockers contraindicated or not tolerated)	IIa C	I B (only verapamil)
Oral diuretics (dyspnoea despite the use of beta-blocker and/or verapamil)	IIa C	IIa C
ACEi or ARBs (LVEF <50%)	IIa C	I B
MRA (LVEF <50% and persisting symptoms despite other HF treatments)	IIa C	–
Atrial fibrillation		
Ventricular rate control		
Beta-blockers (bisoprolol or carvedilol if LV systolic dysfunction)	I C	I C
Verapamil/diltiazem (only with preserved LVEF)	I C	I C
Digoxin (only with LVEF < 50%, no LVOTO and symptoms)	IIb C	–
Prevention of cardioembolic events		
Oral anticoagulant agents (independent of CHA_2DS_2-VASc score/also after a single episode)	I B	I C
NOAC	I B (as second option)	I C (as second option)
Prevention of recurrences		
–Amiodarone	IIa B	IIa B
–Sotalol		IIb C
–Disopyramide (in presence of LVOTO in association with beta-blockers or verapamil)	IIb C	IIa B (also without LVOTO)
Ventricular arrhythmias		
Reduction of the occurrence of NSVT		
Amiodarone	–	–
Sotalol	–	–
Reduction of symptomatic VT or recurrent shocks (with ICD)		
Amiodarone	I C	–
Beta-blockers	I C	–

A, age 65–74 years; A2, age ≥75 years; ACEi, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CHA_2DS_2-VASc, C, congestive heart failure (or left ventricular systolic dysfunction); D, diabetes mellitus; H, hypertension; LV, left ventricle; LVEF, left ventricular ejection fraction; LVOTO, left ventricular outflow tract obstruction; MRA, mineralocorticoid receptor antagonist; NOAC, new oral anticoagulants; NSVT, non-sustained ventricular tachycardia; S, prior stroke or TIA; Sc; sex category (i.e. female sex); V, vascular disease.

Disopyramide (an antiarrhythmic class IA agent) can be used in association with beta-blockers to improve symptoms and reduce intraventricular gradients in patients with LVOTO by virtue of its negative inotropic effect.[11] Whereas beta-blockers are most effective on provokable LVOTO, disopyramide is the most effective agent on resting obstruction.[29] Efficacy and safety of disopyramide have been demonstrated in a large multicentre registry.[30,31] However, QT prolongation and its anticholinergic properties can limit its use and impair compliance. The latter include xerostomy, accommodation disturbances and, in men, lower urinary tract symptoms/prostatism, which may be treated with low doses of pyridostigmine.[32] Moreover, disopyramide tends to lose its efficacy over time. Therefore, in our experience, it often represents a pharmacological 'bridge' to invasive septal reduction therapies, rather than a long-term strategy. An electrocardiogram (ECG) should be performed before initiation of the drug, to evaluate the corrected QT (QTc) interval. Sustained-release 250 mg tablets are the usual choice, at a starting dose of 125 mg twice daily. After the first week, QTc is re-evaluated before disopyramide is titrated to the full dose (250 mg twice daily). It is essential to inform patients of the need to avoid concomitant therapy with other drugs associated with QTc prolongation; conditions that favour dehydration or electrolyte imbalance should also be avoided. In patients who are intolerant to disopyramide, cibenzoline has been employed by Japanese authors, with beneficial effects on dynamic obstruction and LV diastolic function.[33] Serial evaluation of the resting outflow gradient is important during the titration of the pharmacological therapy, although drug titration should proceed if tolerated even when systolic anterior movement is abolished, as obstruction is likely to recur on effort. Exercise echocardiography should be performed when the optimal regimen is reached, in order to exclude residual provokable gradients.

In patients with LVOTO and concomitant disease requiring pharmacological treatment, caution is required with vasodilators and/or positive inotropic agents, because of the risk of exacerbation of LVOTO; examples include phosphodiesterase

type 5 inhibitors for the treatment of erectile dysfunction, methamphetamine for attention deficit hyperactivity disorder, angiotensin-converting enzyme inhibitors (ACEi), or angiotensin receptor blockers (ARBs) for treatment of concomitant systemic hypertension. Nevertheless, these drugs often seem well tolerated.[9,34,35]

In the presence of asymptomatic patients with high resting or provokable gradients, one should always question the true lack of symptoms vs. lifestyle adaptation. These patients often have demonstrable exercise limitation, which is exacerbated by meals. Furthermore, severe gradients may be associated with haemodynamic instability and abnormal blood pressure response on effort. Based on these considerations, a course of pharmacological therapy aimed at controlling outflow obstruction may lead to subjective improvement even in 'asymptomatic' patients, and is likely to provide greater haemodynamic balance during daily activity. If well-tolerated and effective, treatment may be continued based on patients' preferences.

Prophylaxis for endocarditis is advised limited to patients with LVOTO, when invasive medical procedures are required.[36,37] However, risk is low, and neither the 2014 ESC guidelines nor the 2011 American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines on HCM specifically recommended prophylaxis.[11,12] However, these considerations should be weighed against recent data suggesting an association between decreased use of antibiotic prophylaxis in general cardiac patients and an increased incidence of endocarditis, both in high- and low-risk individuals.[38]

Treatment of non-obstructive patients and progressive disease

In patients with preserved LV ejection fraction (LVEF), symptoms may be associated with diastolic dysfunction or microvascular ischaemia. However, the presence of severe refractory symptoms consistently elicited by exercise should raise suspicion of labile obstruction, and be specifically investigated. Dyspnoea and angina in non-obstructive patients can be usually controlled by beta-blockers,[11] employing the same agents used for LVOTO although usually at lower doses. In patients with non-obstructive HCM, titration of beta-blockers follows the aforementioned patterns, although lower doses are generally required in view of a less pronounced adrenergic drive. Symptomatic response and tolerability should drive titration, rather than specific instrumental parameters. Diastolic indices, in particular, appear of little value in this setting. Notably, in the small subset with end-stage disease, whether owing to systolic dysfunction or restrictive evolution, the armamentarium and modalities of classic HF is required. Titration of beta-blockers should be more cautious in these patients because of the fragile haemodynamic equilibrium. Diltiazem or verapamil may be used as an alternative.[11] Verapamil has been the most widely applied therapy in HCM and, although a clear benefit in improvement of functional capacity has never been demonstrated, it may be effective in improving quality of life, likely because of its ability to slow heart rate and prolong LV ventricular filling time. The dose ranges from 60 mg twice daily to 240 mg twice daily. Similar effects are observed with diltiazem (dose range 120–360 mg/day) (*Tables 1* and *2*).

In HCM patients with angina or atypical chest pain, no drug has shown convincing efficacy in improving microvascular function. In clinical practice, symptomatic relief may be obtained by classic anti-ischaemic agents. The most effective are usually represented by AV blocking drugs such as beta-blockers and verapamil. This is consistent with an early observation by Cannon *et al.*[39] showing that high ventricular rates are associated with lactate release in the coronary sinus in HCM patients (i.e. with ischaemia). In our experience, ranolazine can also be very effective in controlling chest pain,[40] although individual response may be variable. Finally, long-acting nitrates and dihydropyridines may be employed as second-line agents, but are usually less effective unless there is associated coronary artery disease.[41]

Up to 10–15% of patients with HCM develop signs and symptoms of HF despite preserved systolic function, with worsening diastolic indices subtended by extensive myocardial fibrosis (*Figures 2* and *3*). Of these, about one-third develop frank LV restriction and/or systolic dysfunction, evolving to refractory HF and the so-called 'end-stage' of HCM.[13,14] Standard HF therapy should be systematically introduced if LVEF $< 50\%$,[42] including ACEi, ARBs, beta-blockers, mineral-corticoid receptor antagonists, and loop diuretics (Class IIa, LOE C).[11] Considering that HCM is generally characterized by a small LV cavity and supranormal systolic function, even LVEF values in the low-normal range should be regarded with suspicion. Indeed, previous work from our groups based on cardiac magnetic resonance (CMR) has shown that average LVEF in resting conditions exceeds 70% in HCM patients, and that values in the 50–65% range may be already subtended by significant amounts of myocardial fibrosis, suggesting that progression towards end-stage disease may have begun.[43] Thus, in selected patients within this LVEF range, it is reasonable to consider HF treatment with ACEi, ARBs, mineralocorticoid receptor antagonists, and loop diuretics in the presence of congestive symptoms as evidence of increasing LV filling pressure and/or extensive myocardial fibrosis. Cardiac resynchronization therapy (CRT) has been employed in the setting of systolic dysfunction with concomitant left bundle branch block (Class IIb, with LOE C recommendation on CRT), although a survival benefit has not been demonstrated.[11] Definitive indications for CRT in end-stage HCM are still lacking and the predictors of response are likely different from those applied in HF, beginning with the higher LVEF threshold requiring consideration in HCM.[11]

Although cardiac transplant is rarely performed in HCM, patients have an excellent outcome (Class IIa indication for patients with LVEF $<50\%$ and Class IIb for patients with LVEF $\geq 50\%$, both LOE B).[11] When disease progression is evident, referral to transplantation centres should be prompt, as the window of opportunity may be lost because of rapidly ensuing, refractory pulmonary hypertension. The use of LV assist devices has been reported in HCM, but can be challenging because of the small LV dimensions observed in most end-stage patients (Class IIb, LOE C).[11]

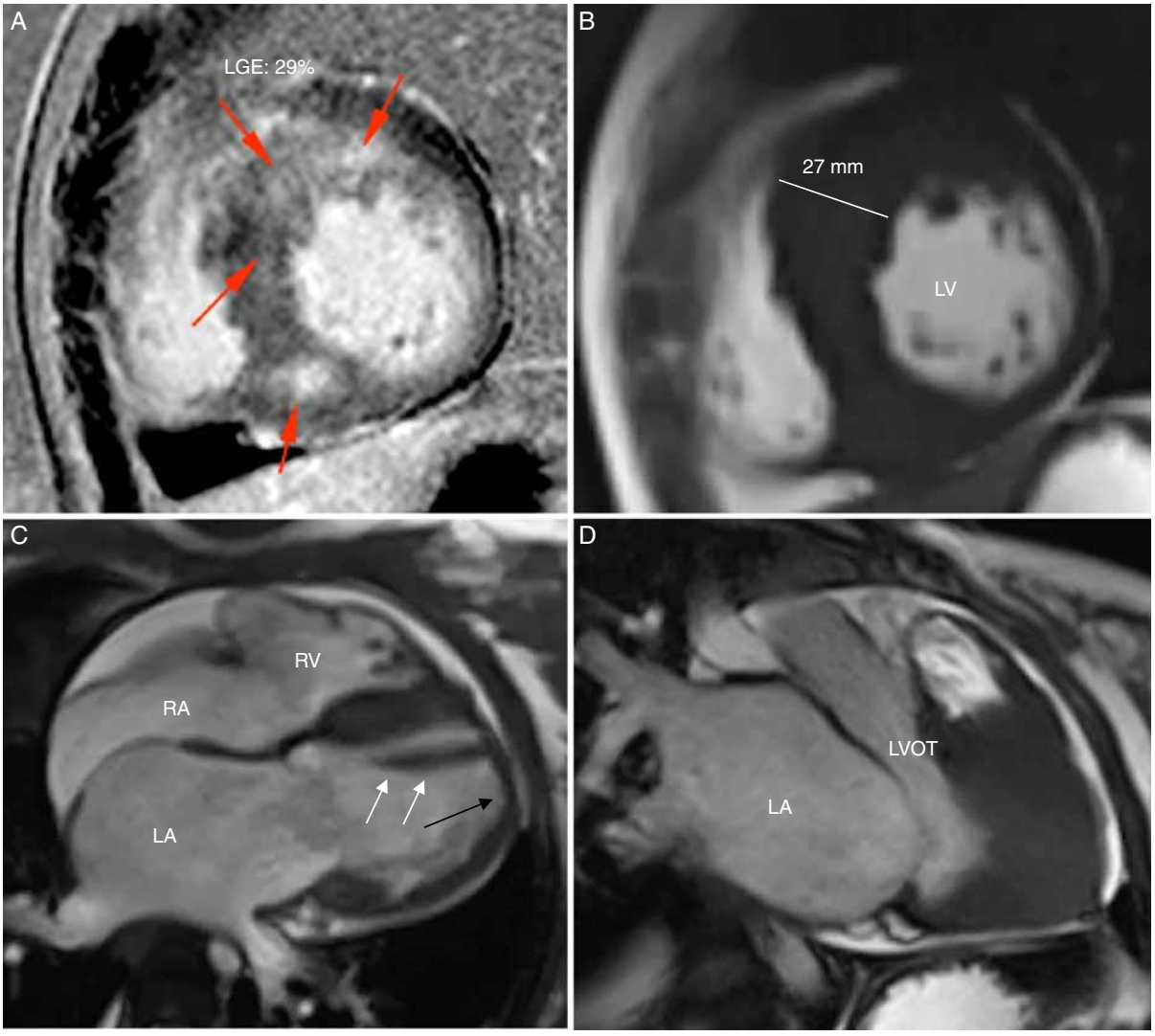

Figure 3 Cardiac magnetic resonance of a 15-year-old Caucasian female patient with non-obstructive hypertrophic cardiomyopathy, presenting with severe heart failure symptoms (New York Heart Association class III) despite preserved left ventricular (LV) ejection fraction (67%). There was evidence of severe pulmonary hypertension, restrictive LV filling pattern and moderate mitral valve insufficiency. She subsequently required heart transplantation (HTx). Ambulatory medical treatment before admission for HTx included atenolol 100 mg once daily, furosemide 25 mg twice daily, acetylsalicylic acid 100 mg and ivabradine 5 mg once daily (off-label use to control sinus tachycardia). (A) Extent of late-gadolinium enhancement (LGE—mainly located at the anterior and posterior insertion of the right ventricle free wall—red arrows) constituting 29% of the LV, compatible with extensive fibrotic replacement. (B) Short axis view showing asymmetric distribution of hypertrophy; LGE is observed at the site of maximum LV thickness. (C) Four-chamber view showing marked dilatation of the left atrium (LA, area 39 cm^2) and a dysmorphic LV with apically displaced papillary muscle (white arrows) inserted at the level of an 'amputated' apex (black arrow). (D) No evidence of dynamic obstruction at the LV outflow tract (LVOT). RA, right atrium. (Courtesy of Patrizia Pedrotti; Niguarda Ca' Granda Hospital, Milan, Italy).

Management of atrial fibrillation

Atrial fibrillation is the most frequent arrhythmia in HCM, affecting more than 20% of patients, and represents a marker of unfavourable prognosis, particularly when associated with LVOTO and in patients younger than 50 years of age; moreover, the onset of AF worsens symptoms related to HF.[44–46] Following onset of paroxysmal AF, long-term antiarrhythmic therapy is generally employed to prevent recurrences (*Tables 1* and *2*). Sotalol and, in patients with LVOTO, disopyramide (associated with beta-blockers) represent reasonable first-line agents while other Class I agents, such as flecainide or propafenone, are generally avoided owing to concerns with pro-arrhythmic effects and haemodynamic deterioration because of conversion to AF with rapid ventricular conduction.[11] Significant clinical experience with dronedarone is lacking. When AF relapses in the context of HF

or LVOTO with severe left atrial dilatation, amiodarone represents the only option for rhythm control. Furthermore, the 2014 ESC guidelines on HCM recommend the use of amiodarone following DC cardioversion (Class IIa, LOE B).[11] Owing to concerns with long-term toxicity in young patients, the minimum effective dose should be employed (usually, 200 mg five to seven times per week) and regular surveillance for thyroid, hepatic, pulmonary, and ophthalmic toxicity should be instituted. Symptomatic AF refractory to optimal pharmacological therapy represents an indication for transcatheter ablation of AF (or surgical maze in obstructive patients undergoing surgery). However, international experience in HCM is limited. In the selection of eligible patients to this procedure it must be considered that high recurrence rates are expected in older patients with advanced symptoms and marked left atrial dilatation.[47] Thus, AF ablation should be considered early following onset of AF until the arrhythmic substrate remains amenable. Furthermore, it is important to inform patients that in over 50% a second procedure is necessary for optimal results and that it may not be possible to abandon long-term antiarrhythmic therapy.[47–49]

When maintenance of sinus rhythm is not deemed feasible and rate control is the only option, beta-blockers (atenolol, nadolol, metoprolol, or bisoprolol in the presence of a preserved LVEF, bisoprolol, or carvedilol in the presence of systolic dysfunction) and verapamil or diltiazem (only with preserved LVEF) are indicated.[11] Digoxin should not be used in the setting of classic HCM, but may be considered in the subgroup with advanced LV dysfunction for rate control in the setting of chronic AF. Rarely, an 'ablate and pace' approach is necessary, usually in end-stage patients.

The onset of AF in HCM patients, even after a single episode, constitutes an indication to oral anticoagulation irrespective of other risk factors for embolic stroke such as age or gender. Use of the CHA_2DS_2-VASc score is not recommended:[11] in a retrospective analysis of 4821 HCM patients, 9.8% subjects with a CHA_2DS_2-VASc score of 0 had a thromboembolic event during the 10-year follow up.[50] Furthermore, advanced age, presence of AF, previous thromboembolic event, advanced NYHA class, increased left atrial diameter, presence of vascular disease, and increased maximal LV wall thickness were found to correlate with risk of thromboembolic events, whereas the use of vitamin K antagonists was associated with a 54.8% relative risk reduction in HCM patients with AF.[50] Warfarin represents the drug of choice and should be titrated to maintain an international normalized ratio (INR) between 2.0 and 3.0. However, many young and active patients show limited compliance with this regimen or refuse it altogether, while others may have difficulties in maintaining the INR within the therapeutic range or experience complications.[45] Until recently, the less effective alternative of an antiplatelet agent was offered; however, the introduction of the novel oral anticoagulants (NOACs), including the direct thrombin inhibitor dabigatran and factor Xa inhibitors rivaroxaban, apixaban and edoxaban, is rapidly changing this landscape. While caution is mandatory in the absence of safety and efficacy data in HCM patients, NOACs appear a promising alternative to warfarin, and deserve specific investigation.[11]

Control of ventricular arrhythmias

An ICD is considered the only effective strategy for prevention of arrhythmic SCD in patients with HCM. The ICD is universally recommended in secondary prevention, as the risk of arrhythmic relapse after the first episode is as high as 11% per year (Class I, LOE B).[11,51] Conversely, indications for primary prevention are hotly debated. A new score has recently been developed by the ESC,[25] by which a high risk is defined as ≥6% at 5 years. The score is currently being validated in independent cohorts, with contrasting results.[52–54] Conversely, the ACCF/AHA guidelines favour individual, non-parametric evaluation of major risk factors.[12] The issue of the prevention of SCD and arrhythmic risk stratification is beyond the scope of the present review. The issue remains central to HCM management, and has been the focus of several articles in the recent literature.[15,55] Classic and emerging risk factors, such as late-gadolinium enhancement and complex genotypes,[56–58] are commonly used to assess risk in individual patients, with approaches that slightly differ in Europe and the USA (see the Supplementary material online, *Table S1*). Irrespective of any chosen approach, the identification of high-risk patients remains challenging because of low arrhythmic event rates, limited accuracy of risk factors and stochastic nature of SCD.[59,60] Even in high-risk HCM patients, the onset of life-threatening arrhythmias is highly unpredictable, as highlighted by the variable long time-lapses between ICD implantation and first appropriate intervention. Notably, neither a circadian trend in the onset of ventricular arrhythmias nor a significant correlation with strenuous exercise has been documented.[61] The vast majority of patients with an ICD will never experience appropriate shocks, but will be exposed to the long-term complications of the device.[51] Furthermore, while paediatric cohorts are considered at highest risk, older age is associated with a marked reduction in the likelihood of SCD. The risk of SCD is markedly reduced over 65 years of age, and fewer indications for ICD implantation in primary prevention exist in this age group. Nevertheless, the option must be evaluated on an individual basis and considered in patients with multiple risk factors. End-stage progression with systolic dysfunction (arbitrarily but consistently defined in the literature by a LVEF <50%) is associated with a high risk of SCD (around 10% per year) and therefore considered an indication for ICD implantation in primary prevention.[14,62] However, consideration for an ICD should be given also to patients with preserved systolic function in the presence of severe diastolic impairment (restrictive evolution) associated with NYHA functional class III symptoms.

Several studies show that empirical pharmacological treatment does not confer optimal protection against SCD (*Table 2*). Nonetheless, amiodarone, sotalol, and beta-blockers reduce the occurrence of non-sustained ventricular tachycardia.[12,63] Thus, it is likely that a judicious pharmacological approach can be effective in reducing the arrhythmic burden and risk in patients with HCM, as well as reducing the incidence of appropriate ICD interventions. In our experience the combination of nadolol with low-dose amiodarone is well tolerated and effective in reducing ventricular arrhythmic burden, as documented by ECG Holter monitoring,

Table 3 Drugs that have been employed in different preclinical studies and/or pilot clinical trials as possible disease-modifying therapies in hypertrophic cardiomyopathy (HCM)

Drug	Diltiazem	Ranolazine/ eleclazine	Losartan/valsartan	Statins	Antioxidants (*N*-acetyl-cysteine)
Molecular target	L-Type Ca channel of CMs	Late Na current of CMs	AT1-receptor blockers on CMs and myocardial FBs	HMG-CoA reductase	Precursor of glutathione (antioxidant)
Proposed mechanism	Reduced Ca entry into the cytosol of CMs, causing ↓ $[Ca]_i$	Reduced $[Na]_i$ and increased Ca exit from CMs via NCX, causing ↓ $[Ca]_i$	Block of AT1 signalling pathway in CMs (↓hypertrophy) and FBs (↓fibrosis)	↓ Rho/Ras in FBs (↓fibrosis) and in CMs (↓hypertrophy); ↓ oxidative stress	↓oxidative stress in FBs (↓fibrosis) and CMs (↓hypertrophy)
Preclinical studies in HCM models	Preventive treatment in transgenic mice with R403Q β-MyHC mutation[71]	Study on septal samples from HCM patients (myectomy)[71]	Losartan in transgenic mice with R92Q-TnT mutation[72]	Atorvastatin in a rabbit model with R403Q MyHC mutation[73]	Rabbits with R403Q MyHC mutuation;[75] mice with TPM mutation[76]
Effects in preclinical studies	Prevention of hypertrophy and LV dysfunction[10]	Reduction of cellular arrhythmogenesis, improved diastolic function[71]	Endomyocardial fibrosis is greatly reduced after treatment[72]	Reduction of hypertrophy and increased LV function[73]	Reduction of hypertrophy, fibrosis[75] and diastolic dysfunction[76]
Clinical studies	Slowing of phenotype development in young mutation carriers[10]	Ongoing studies (RESTYLE-HCM with ranolazine; LIBERTY-HCM with eleclazine)	Losartan in two studies, 33 and 9. Reduced LVH in 33, but no effects on LVH in 9	Pilot study on 32 patients; no effects on hypertro-phy/cardiac function[74]	Ongoing Phase 1 study (NCT01537926)
Future perspective	Increase the number of carriers, prolong follow-up	Prevention of phenotype development in transgenic mice	VANISH study for prevention of phenotype in HCM mutation carriers	None	Ongoing Phase 1 study (NCT01537926)

AT1, angiotensin II receptor type 1; β-MyHC, β-myosin heavy chain; Ca, calcium; $[Ca]_i$, calcium inward current; CMs, cardiomyocytes; FBs, fibroblasts; HMG-CoA, 3-hydroxy-3-methyl-glutaryl-CoA; LV, left ventricular; LVH, left ventricular hypertrophy; Na, sodium; $[Na]_i$, sodium inward current; NCX, sodium–calcium exchanger; TnT, troponin-T; TPM, tropomyosin. Superscript numbers in the table are references.

potentially contributing to the low incidence of SCD at our institution in the pre-ICD era (0.5% per year).[64]

When not to treat

Patients with HCM who are asymptomatic and have no evidence of arrhythmias or LVOTO at rest or on effort generally do not require medical treatment. However, some patients self-reporting as asymptomatic may subjectively benefit from low doses of beta-blockers (e.g. bisoprolol 2.5 mg once daily), particularly on effort and after meals. Treatment should be offered as a short (2–3 months) trial, after which each subject may decide whether to continue. As a rule, it is good to investigate whether the patient is truly asymptomatic, by performing maximal, symptom-limited exercise testing and assessing biomarkers over time. Labile obstruction should also be excluded. In the case of adolescents and very young adults exercising regularly, heart rate control using beta-blockers may be considered in order to avoid elevated cardiac rates on effort, which are associated with lactate production in HCM hearts, reflecting silent ischaemia.[39]

Aggressive control of modifiable cardiovascular risk factors is mandatory in HCM patients, in order to prevent the synergistic effects of coronary disease, diabetes and hypertension.[41] Management of hypertension should follow existing guidelines.[65] Although the introduction of vasodilators should be cautious and gradual, because of potential worsening of resting or labile LVOTO, recent trials have shown that ARBs are safe and generally tolerated in HCM patients.[9,34] Finally, patients with obstructive HCM have a significant prevalence of obstructive sleep apnoea syndrome; this may exacerbate symptoms and arrhythmias and should be specifically sought and managed.[66] Advice regarding appropriate lifestyle maybe extremely useful in reducing symptoms and risk in HCM patients, and may suffice in milder forms of the disease in which pharmacological therapy is not warranted. There is general consensus that patients should abstain from competitive sports, as well as from strenuous and prolonged physical activity, which can represent a trigger for arrhythmias and SCD (Class I, LOE C in the 2014 ESC guidelines).[11] Conditions that reduce circulating blood volume should be avoided to prevent worsening of LVOTO.[67]

Table 4 Ongoing and completed randomized clinical trials assessing efficacy and safety of medical agents in patients with hypertrophic cardiomyopathy (HCT) since 2010

First Author or Name of the study	Drug on evaluation	Endpoint of the study	Number of patients	Results	Year of publication
Abozguia *et al.*[69]	Perhexiline 100 mg vs. placebo	Efficacy on diastolic function and exercise capacity	46 patients with non-obstructive symptomatic HCM	The metabolic modulator perhexiline improved diastolic function and increased peak oxygen uptake	2010
Shimada *et al.*[34]	Losartan 50 mg bid vs. placebo	Effects on LVH and fibrosis	20 patients with non-obstructive HCM	Attenuation of progression of LVH and fibrosis with losartan	2013
INHERIT trial[9]	Losartan 100 mg vs. placebo	Effects on LVH and fibrosis	124 patients with obstructive or non-obstructive HCM	Losartan did not reduce LVH. Treatment with losartan was safe	2015
Ho *et al.*[10]	Diltiazem 360 mg/die vs. placebo	Safety, feasibility and effect of diltiazem as disease-modifying therapy	38 sarcomere mutation carriers without LVH	Diltiazem improved early LV remodelling	2015
–	Perhexiline 100 mg (sponsor: Heart Metabolics Ltd) vs. placebo	Hierarchical classification of outcome variable and change in maximum oxygen consumption after 6 months	320 patients with HCM and moderate to severe HF	Phase III	Starting March 2016 (NCT02431221)
RESTYLE-HCM[†]	Ranolazine	Change in maximum oxygen consumption at CPET	80 patients	Phase II/III	Ongoing—completed recruitment
LIBERTY-HCM	GS-6615 (sponsor: Gilead Sciences) vs. placebo	Safety/efficacy study on exercise capacity in pts with symptomatic HCM	180 patients with HCM	Phase II/III evaluation of change in peak oxygen uptake	Ongoing—recruiting patients NCT02291237
VANISH (New England Research Institute, USA)	Valsartan up to 160 mg vs. placebo	Composite endpoint of functional capacity, amount of myocardial fibrosis and other parameters after 2 years	150 patients HCM in NYHA class I–II and mutation carriers without LVH	Phase II	Ongoing–recruiting patients (NCT01912534)
University of Texas, Health Science Centre, Houston, USA	*N*-acetyl-cisteine 600/1200 mg vs. placebo	Regression of indices of cardiac LVH after 3 years	75 patients with HCM and preserved systolic function	Phase I	Ongoing—recruiting patients (NCT01537926)

CPET, cardiopulmonary exercise test; HCM, hypertrophic cardiomyopathy; HF, heart failure; LV, left ventricular; LVH, left ventricular hypertrophy; NYHA, New York Heart Association.

[*]With updated data on clinicaltrials.gov (key word: 'hypertrophic cardiomyopathy', selected on 116 studies) and pubmed.org (Key words: 'hypertrophic cardiomyopathy' AND 'clinical trials' from 2010: 143 results). No updated data were available regarding clinical trials testing the efficacy of pirfenidone 400 mg b.i.d. (completed recruitment in 2003, NCT00011076) and atorvastatin 80 mg (completed recruitment in 2010, NCT00317967). RHYME study is a non-randomized study registered in clinicaltrials.gov aimed to test efficacy of ranolazine in reducing angina symptoms after 60 days in 20 patients (NCT01721967).

[†]Study registered in EU Clinical Trials Register, EudraCT Number: 2011-004507-20.

Novel perspectives

A surge in pharmacological research on HCM has followed the identification of novel therapeutic targets, and holds promise for a rapid change in clinical management of this disease. Several molecular mechanisms and disease pathways, stemming from the genetic background of HCM, represent appealing therapeutic targets, and have been reviewed by Ashrafian *et al.*[68] Indeed, based on sound translational research, a number of agents have already found their way to clinical testing. Perhexiline, a metabolic modulator that inhibits the metabolism of free fatty acids and enhances carbohydrate utilization by cardiomyocytes, has been employed with the aim of normalizing energy homeostasis in HCM. In a randomized, double-blind placebo-controlled trial, perhexiline has shown the capacity to improve the ratio of myocardial phosphocreatine to adenosine triphosphate in the myocardium, resulting in improved diastolic function and exercise capacity.[69] A randomized, pivotal Phase 3 trial of 350 patients evaluating perhexiline for the treatment of moderate-to-severe HCM has recently been announced (http://www.heartmetabolics.com/news/2015/news-041515.html). However, concerns exist regarding the safety profile of the drug, following reports of hepatotoxicity in predisposed individuals, and the drug requires long-term monitoring of plasma levels.[70]

Recently, human HCM cardiomyocytes have been shown to exhibit marked electrophysiological remodelling leading to abnormal intracellular calcium handling, enhanced arrhythmogenesis, abnormal diastolic function, and excessive energy expenditure. These defects are selectively reversed *in vitro* by the late sodium current inhibitor ranolazine.[71] Thus, targeting this single molecular mechanism has the potential to counter several key components of the HCM pathophysiology, including diastolic dysfunction, microvascular dysfunction, arrhythmogenesis and, by virtue of mild negative inotropic effects, dynamic outflow obstruction.[71] These data provided a rationale for the recently completed multicentre, double-blind, placebo-controlled pilot study testing the efficacy of ranolazine on exercise tolerance in symptomatic HCM patients (RESTYLE-HCM, study registered in EU Clinical Trials Register, EudraCT Number: 2011-004507-20; https://www.clinicaltrialsregister.eu/ctr-search/trial/2011-004507-20/DE). While results of RESTYLE-HCM are awaited, a phase II/III trial, the LIBERTY-HCM study, has already started testing the efficacy of a new, more specific and potent late sodium current inhibitor, eleclazine (Clinicaltrials.gov NCT02291237). LIBERTY-HCM will test the hypothesis that, compared with placebo, eleclazine improves exercise capacity as measured by peak oxygen consumption (VO_2) during cardiopulmonary exercise testing in patients with symptomatic HCM from over 40 centres in Europe and the USA. Additional drugs that have been employed in different preclinical studies and/or pilot clinical trials as possible disease-modifying therapies in HCM are listed in *Tables 3* and *4* and include angiotensin II type 1 (AT1)-receptor blockers losartan and valsartan,[9,58,72] statins,[73,74] and *N*-acetyl-cysteine.[75,76]

Finally, a 'precision medicine' approach is emerging based on the hypothesis that, in selected genetic subsets, HCM is triggered by a hypercontractile state caused by reduced inhibitory effect of the myosin-binding protein C on the cardiac myosin head. By selectively reducing the affinity of myosin for actin, the downstream consequences of sarcomere mutations might be countered in HCM patients, including prevention of phenotype development in the early stages of the disease.[77] Two phase I studies have been recently launched to assess the effects of MYK-461 (Myokardia, South San Francisco, CA, USA), the first allosteric inhibitor of cardiac myosin tested in man, in patients with HCM (Clinicaltrials.gov NCT02329184 and NCT02356289).

Conclusions

Hypertrophic cardiomyopathy largely remains an orphan disease. In the near future, however, the debut of evidence-based approaches to HCM is likely to revolutionize its management by providing agents targeting disease-specific substrates. Until then, judicious use of the available pharmacological armamentarium may already provide sufficient control of the most common clinical manifestations and complications, allowing normal longevity in the majority of patients. Serial assessment and early identification of disease progression is key for timely implementation of available therapies.

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Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Risk factors for sudden cardiac death in hypertrophic cardiomyopathy according to the 2014 European Society of Cardiology and 2011 American College of Cardiology Foundation/American Heart Association guidelines.

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