An Overview of Pharmacotherapy in Hypertrophic Cardiomyopathy: Current Speculations and Clinical Perspectives

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Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiac disease. Its clinical course is variable, ranging from a benign asymptomatic or mildly symptomatic course throughout life, to severe symptoms (dyspnea, angina, palpitations) or cardiovascular events (syncope and thromboembolism). Sudden cardiac death (SCD) remains the most striking manifestation of the disease, affecting a minority of patients. This review focuses on the medical treatments applied according to the symptomatology in obstructive and nonobstructive HCM; a special reference is made to atrial fibrillation and arterial hypertension, which often coexist with the disease. Current literature about the pharmaceutical prevention of SCD is also analyzed and novel pharmacologic agents and approaches that may represent the future management of HCM are critically reviewed. The analysis of interventional techniques that are used in cases of medical treatment failure is avoided. Rather than enumerating clinical studies and guidelines, this review provides a concise and contemporary analysis of HCM pharmacotherapy, developing applicable algorithms for clinicians and highlighting promising future drug regimens.

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KEY WORDS

Hypertrophic cardiomyopathy • Medical treatment • Left ventricular outflow tract obstruction • Sudden cardiac death

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiac disease, with a prevalence of 0.2% in the general population.[1,2] The disease is characterized clinically by unexplained left ventricular (LV) hypertrophy, histologically by myocyte disarray, and interstitial and replacement fibrosis, the latter developing in more advanced stages of the disease. Its clinical course is quite variable, ranging from a benign asymptomatic or mildly symptomatic course throughout life, to severe symptoms (dyspnea, angina, palpitations) and cardiovascular events (such as syncope and thromboembolism). Sudden cardiac death (SCD) remains the most striking manifestation of the disease, affecting a minority of patients.[1,2]

The major factors that determine the severity of symptoms in HCM are LV outflow tract (LVOT) obstruction,[3] atrial fibrillation (AF),[4] diastolic dysfunction,[5] and myocardial ischemia.[6] Mitral regurgitation, if present (but not to the magnitude of LV hypertrophy, which constitutes a risk factor for SCD),[7] may also contribute to the severity of symptoms. Approximately 40% of patients are asymptomatic at the time of diagnosis, and proceed to screening primarily due to a family history of HCM, an abnormal electrocardiogram (ECG) result, or an audible cardiac murmur.[8]

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Medical Management of Asymptomatic HCM Patients

In asymptomatic patients with HCM who have normal functional capacity and a reassuring arrhythmic profile, no drug treatment is recommended, regardless of the existence of LVOT obstruction. Clinical screening of first-degree relatives and other family members is encouraged. Patients should be discouraged from participating in intense competitive sports and should be properly educated to recognize and prevent other cardiovascular diseases (eg, quit smoking and alcohol abuse, control dyslipidemia and diabetes, and avoid complete physical inactivity) that may deteriorate their clinical condition. A thorough follow-up and detection of coronary disease is also highly suggested. Additionally, when treating asymptomatic patients with LVOT obstruction, the risk of the sudden onset of symptoms should be pointed out as a result of dehydration, and vasodilator and diuretic use, due to coexisting hypertension. Finally, risk stratification for SCD is recommended in all patients with HCM, regardless of the existence of symptoms.

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Pharmacotherapy for Symptomatic Patients

The fundamental goals of treatment in symptomatic patients with HCM are the alleviation of symptoms and the relief or reduction of the LVOT gradient if present. Of note, only 30% of HCM patients do not present with LVOT obstruction at rest or during exercise,[9] and, although symptoms may exist in patients without obstructive disease, medical therapy is mainly referred to patients with obstruction.

β-Blockers are considered to be the first-line treatment, especially those agents that do not cause peripheral vasodilatation which may further worsen the obstruction in LVOT. Pronethalol, an early abandoned β-blocker, was the first drug that was found to blunt or abolish the increase in gradient caused by isoproterenol or by exercise. The drug was never used in clinical practice due to severe side effects.[10,11] After that, propranolol was found to improve symptoms and ameliorate exercise-induced obstruction; from a clinical point of view it was established as a standard therapy in obstructive HCM for many years.[12-16] In one study, administration of propranolol in high doses (5-23 mg/kg/d) in children and teenagers (aged < 19 years) with HCM with or without LVOT obstruction was associated with prolonged survival.[17]

At present, the most frequently used β-blockers are bisoprolol (5-10 mg/d), atenolol (50-100 mg/d), metoprolol (50-100 mg/d), and nadolol (40-80 mg/d); the use of propranolol is restricted only to children according to the results of a study by Ostman-Smith and colleagues.[17] In another clinical trial in patients with mild or moderately symptomatic HCM, nadolol or verapamil did not demonstrate a significant effect on exercise capacity, although there was a tendency to improve symptoms; verapamil

appeared to be superior to nadolol in this regard.[18] In a small clinical trial in patients with HCM and obstruction only during exercise, the use of bisoprolol or nadolol relieved the obstruction in 52% of the patients, reduced it significantly in 33%, and had no effect in 15% of the patients.[19] Similar results have been reported in a previously published trial with bisoprolol.[20] The value of administrating β-blockers in symptomatic patients with obstructive HCM is highly documented. However, although their effect on reduction or complete elimination of dynamic obstruction is indisputable, their effect on the reduction of obstruction under resting conditions is weaker.[19,20] Additionally, data on the impact of β-blockers on the long-term outcome of HCM patients are lacking. In nonobstructive HCM, the beneficial effect of β-blockers is mainly mediated by the slowing of the heart rate and the prolongation of the LV diastolic period.

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Some experts suggest verapamil or diltiazem as first-choice therapeutic agents; their positive effects originate from negative inotropic and chronotropic action that leads to prolongation of the diastolic period and redistribution of flow toward the subendocardium. Verapamil, first applied as an alternative to propranolol at a dose of 480 mg/d, improved symptoms in the majority of patients with obstructive HCM.[21,22] Rosing and colleagues, in two reports, found a beneficial effect on acute gradient reduction and improvement of symptoms in long-term follow-up, although a substantial number of patients stopped the drug due to severe side effects.[23,24] In another study, verapamil and propranolol were found to have similar beneficial effects on exercise time.[25] Verapamil has also been recorded to be safe and efficacious for acute and chronic treatment in infants with HCM, improving symptoms in patients with or without obstruction.[26]

Diltiazem can be used as an alternative to verapamil, because both drugs share the same hemodynamic profile, although relevant studies on the use of diltiazem in HCM are lacking. Diltiazem likely acts by improving diastolic function[27-32] and ameliorating myocardial ischemia. Additionally, diltiazem may decrease exercise-induced elevated pulmonary artery diastolic pressure.[33] The therapeutic goals of the administered treatment are achievement of a heart rate of approximately 55 to 60 beats/min at rest and the avoidance of symptomatic hypotension.

Unfortunately, the favorable effect of the aforementioned drugs is reversed largely due to peripheral vasodilatation and the augmentation of obstruction that can cause unpredictable and severe hemodynamic instability.[34] The administration of these calcium channel blockers (verapamil or diltiazem) should be used with caution in patients with severe LVOT obstruction, low blood pressure, or high wedge pressure. Conversely, dihydropyridines and especially nifedipine should not be administered in patients with obstruction in LVOT.

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When the symptoms are not controlled despite the use of β-blockers, there are two alternative options: the addition of either verapamil or disopyramide to a β-blocker in case of an obstructive disease. Coadministration of verapamil and a β-blocker should preferably be initiated in a hospital setting because it can further deteriorate LVOT obstruction due to peripheral vasodilatation (although it may cause severe bradycardia and hypotension). According to our opinion, and most experts, this drug combination should be avoided.

The addition of disopyramide to a β-blocker is the optimal drug combination for obstructive HCM with symptoms refractory to β-blockers alone, according to most experts.[35,36] Disopyramide is a type I antiarrhythmic drug that has marked negative inotropic effects by decreasing the inward sodium current of the cardiomyocyte during phase 0 of the action potential, achieving a significant reduction of its upstroke velocity. Previous studies have shown that disopyramide reduces the LV ejection velocity during the first systolic period. As a result, there is reduction of hydrodynamic forces exercised on the mitral valve that cause its traction to the ventricular septum. This action eases or prevents the mitral valve's systolic anterior motion and causes the reduction or even elimination of the pressure gradient.[37] The drug seems to be more effective in reducing the resting gradient than β-blockers or verapamil.[38] Disopyramide is usually administrated in combination with a β-blocker because of the combined negative inotropic effect and the subsequent reduction of the gradient or prevention of its rise during exercise. The drug should not be used alone (without prior

administration of a β-blocker) because it may facilitate a rapid ventricular response in cases of HCM complicated with AF, due to significant reduction of atrioventricular node refractoriness. In case of β-blocker intolerance, coadministration of disopyramide with verapamil or diltiazem is possible with caution.

The efficacy of disopyramide in patients with HCM has been controlled in a multicenter clinical trial, in which coadministration with a β-blocker in 118 patients with symptomatic HCM improved their New York Heart Association (NYHA) functional class and reduced the obstruction by 50% in two-thirds of the patients over a 3-year follow-up. The remaining patients were referred for invasive treatment due to persistent gradient or drug side effects. However, only 5% of the patients needed to discontinue disopyramide because of its anticholinergic actions, whereas no proarrhythmic effects or QT prolongation were observed.[39] Overall survival and sudden death incidence was lower in the group treated with disopyramide compared with patients with obstruction who were not treated with the drug. This result may be explained by the pharmacologic relief or reduction of LVOT obstruction caused by disopyramide. In a clinical trial by Sherrid and colleagues, the coadministration of disopyramide with β-blockers or verapamil in 221 patients with obstructive HCM and uncontrolled symptoms resulted in symptoms alleviation and surgery prevention in 64% of the patients.[40] And Ball and associates reported that over 85% of HCM patients receiving optimal medical therapy were in NYHA class I/II heart failure after a mean follow-up of 7 years compared with 67% at baseline.[41] Disopyramide was administrated in 62% of these patients. Of note, the long-term survival of patients with alleviation of symptoms due to medical therapy was comparable with those patients undergoing invasive treatment.

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The initiating therapeutic dose of disopyramide is 300 mg (100 mg, 3 times daily), followed by a gradual increase up to 600 mg/d. Patients don't need to be admitted to the hospital to start the therapy; there is only a need for periodic ECG recordings to monitor the QT segment. The main concern of the use of this regimen is the prolongation of the QT segment (on ECG) and the anticholinergic actions that can cause side effects such as dry mouth and urinary hesitancy, especially among patients with prostatic hypertrophy. In the study by Sherrid and colleagues, the investigators added pyridostigmine to alleviate the anticholinergic actions of disopyramide and allowed the administration of higher doses with a relatively favorable safety profile.[40] Disopyramide's effect on the QT segment in obstructive HCM appears similar to the effect of other cardiovascular drugs, in which QT prolongation does not increase risk of SCD.[42] However, the avoidance of other medical treatments that can cause QT prolongation is essential and disopyramide should be discontinued in patients who already receive antiarrhythmic therapy, especially class III agents (amiodarone or sotalol).

Diuretics can be added in patients with severe heart failure (NYHA class III or IV) with caution because they can significantly reduce LV preload, exacerbating obstruction and causing severe hypotension. In cases of significant drops in blood pressure, vasopressors (eg, phenylephrine) should be used instead of inotropes (eg, dopamine, dobutamine). Classic medical treatments of systolic heart failure with β-blockers, angiotensin-converting enzyme (ACE) inhibitors, and aldosterone antagonists are used in end-stage patients with nonobstructive HCM. In this setting, diuretics can be also added in the presence of pulmonary or peripheral congestion. A schematic approach of the key regimens used in the treatment of HCM is illustrated in Figure 1.

Treatment of AF

AF is an arrhythmia closely linked to HCM, occurring in approximately 25% of patients, and constitutes a major determinant of symptoms, morbidity, and mortality in patients with the disease.[43,44] Maintaining sinus rhythm in symptomatic AF should be attempted either by pharmacologic means or electrical cardioversion. In many patients, the arrhythmia becomes permanent due to the underlying morphologic distortions (eg, mitral regurgitation, left atrial dilatation). Amiodarone or disopyramide combined with a β-blocker or a calcium antagonist (verapamil or diltiazem) are reasonable therapies to prevent recurrent AF,[45] or to slow the ventricular response in case of

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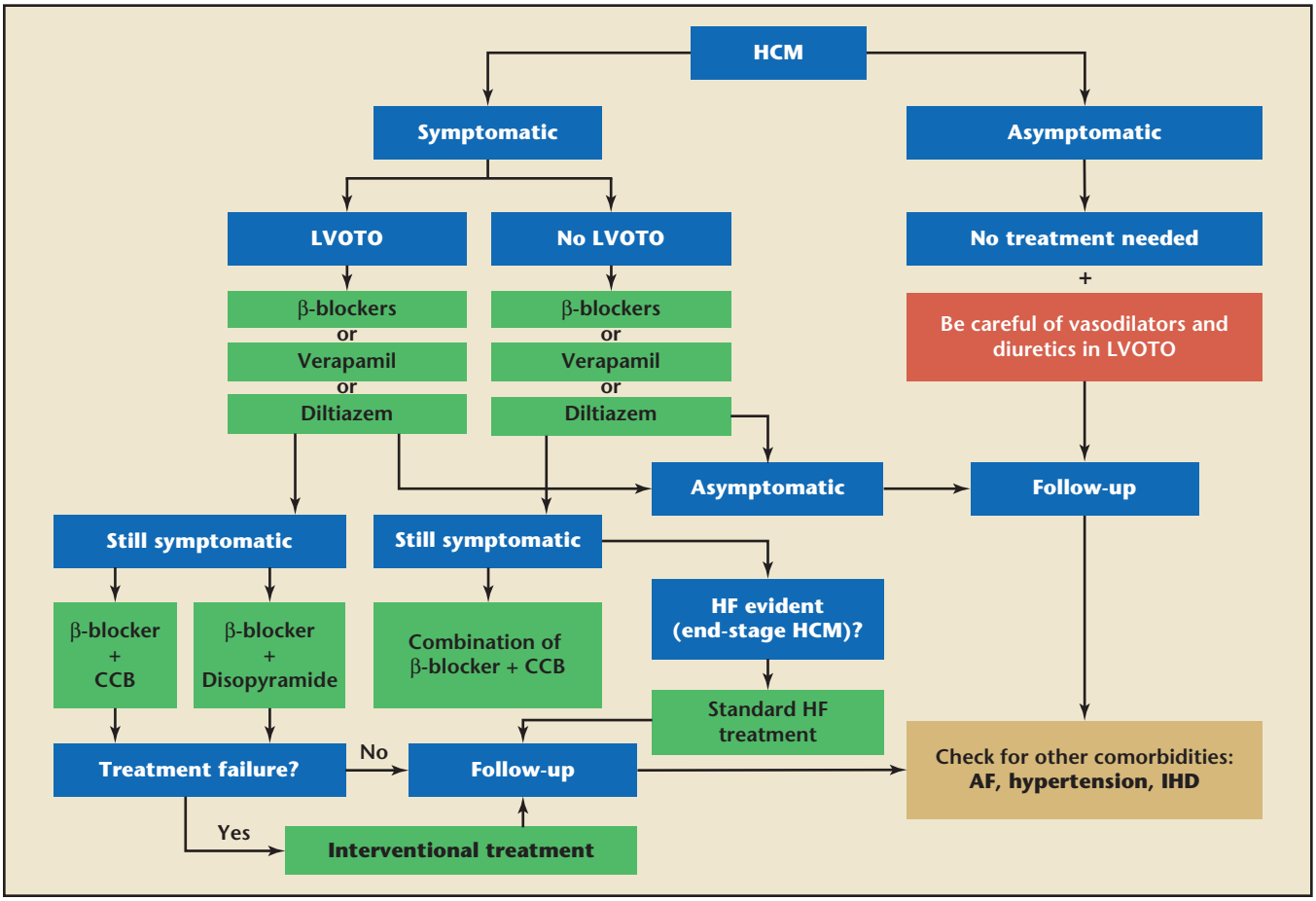

Figure 1. Algorithm for pharmacologic treatment of hypertrophic cardiomyopathy. AF, atrial fibrillation; CCB, calcium channel blocker; HCM, hypertrophic cardiomyopathy; HF, heart failure; IHD, ischemic heart disease; LVOTO, left ventricular outflow tract obstruction.

chronic AF. Digitalis, as a rate control agent, may be coadministered only in nonobstructive cases. In our opinion, even when rate control strategy is adopted, the combination of β-blockers and amiodarone is more appropriate, but requires close monitoring for the possibility of low ventricular response. Sotalol, propafenone, dofetilide, and dronedarone should be avoided in HCM patients with AF due to lack of relevant experience.[46] As previously mentioned, the coadministration of amiodarone and disopyramide should also be avoided due to their combined proarrhythmic effect. In cases of rate control failure, atrioventricular nodal ablation followed by implantation of a permanent pacemaker can be attempted. Results of ablation of the pulmonary veins are encouraging; in one study, two-thirds of patients remained in sinus rhythm for 1 to 2 years.[47] Maze intervention is also considered a reasonable approach for patients undergoing myectomy.

The CHA_2DS_2-VASc (congestive heart failure, hypertension, age $>$ 75, diabetes, stroke, vascular complications, age 65-74, female sex) score has not been validated in HCM patients; however, anticoagulants such as warfarin or acenocoumarol should be administered in cases of AF in order to prevent a possible stroke, even after the first episode.[48] Although empiric administration of novel anticoagulants (direct thrombin inhibitors or factor Xa inhibitors) is also applied in clinical practice, there are no available studies supporting this approach and confirming their safety.

Treating Coexisting Hypertension

Many patients with HCM need antihypertensive treatment, according to the prevalence of hypertension in the general population. In nonobstructive HCM, all classic antihypertensive drugs can be administered, even vasodilators such as ACE inhibitors. A major problem arises in obstructive disease because the administration of vasodilators may exacerbate the obstruction and associated symptoms. Again, β-blockers remain the first choice of antihypertensive treatment. If hypertension is not regulated it is

preferable to add a centrally acting antihypertensive drug, such as clonidine and/or small doses of hydrochlorothiazide.[49]

Prevention of SCD by Administering Drugs

Conventional drugs, such as β-blockers and verapamil, are not proven to prevent SCD in patients with HCM. In a nonrandomized study, administration of amiodarone (mean dose 300 mg/d) in patients who had episodes of ventricular tachycardia (VT) in 24- or 48-hour ECG recordings was accompanied by a reduction of episodes of VT and of the incidence of SCD compared with patients that had received conventional antiarrhythmic therapy with mexiletine, disopyramide, or quinidine.[9] Retrospective data, however, have shown that 30% of patients receiving amiodarone as adjunctive therapy after implantation of an implantable cardioverter defibrillator (ICD) had an appropriate ICD intervention.[50] In another retrospective study, it was shown that SCD or cardiac arrest occurred in 20% of patients receiving amiodarone, in 9% of patients receiving a β-blocker, and in 9% of patients receiving verapamil.[51] Therefore, there is currently no indication for any medication to prevent SCD, with only one possible exception—the administration of amiodarone when ICD implantation is not feasible.[52] Despite the lack of relevant data, however, the administration of amiodarone in patients with frequent ventricular extrasystoles or episodes of nonsustained VT, especially in European countries, is not uncommon.

Preclinical Diagnosis and Early Treatment Potentials

At present, the identification of a group of subjects in the early phase of their disease provides the opportunity to test new therapies to prevent the development of fibrosis, hypertrophy, and dysfunction. It should be emphasized that application of these treatments in the preclinical phase may have a beneficial effect, whereas treatment during a mature phase of the disease could be problematic, because a possible regression of hypertrophy may lead to LV dilation and reduced ejection fraction.[52]

With the knowledge that altered intracellular Ca^{2+} handling occurs early in disease pathogenesis, diltiazem, an L-type calcium channel blocker, produced attenuation of phenotypic development of HCM when administered to young (prehypertrophic) mice carrying a pathogenic myosin heavy chain mutation ($\alpha MHC^{403/+}$).[53] Diltiazem-treated animals developed less LV hypertrophy and histologic disarray and fibrosis than placebo-treated animals. Importantly, the treatment that started after the development of LV hypertrophy was unable to reverse the established phenotype in these animals.[53] In an observational study enrolling a small number (6 patients) of genotype(+)/phenotype(−) HCM patients, oral administration of 240 mg/d of diltiazem led to normalization of early diastolic and systolic velocities approximately 8 weeks after treatment initiation.[54] A recent pilot randomized trial demonstrated that diltiazem improved LV remodelling in preclinical HCM (in subjects with an identified sarcomere mutation and no overt LV hypertrophy).[55] Sufficient data on the effects of diltiazem in preclinical HCM are lacking, but, considering the aforementioned preliminary reports, the drug merits further study.

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Novel Pharmacologic Agents or Novel Approaches in the Management of HCM

Targeting Neurohumoral Activation Secondary to Sarcomere Dysfunction

Angiotensin II is a well-known mediator of hypertrophy and fibrosis in the human heart.[56] This background leads to the hypothesis that angiotensin II receptor blockers can have a potential beneficial effect on HCM. The first studies conducted on animal models of HCM utilizing angiotensin II receptor blockers showed encouraging results. Teekakirikul and colleagues treated prehypertrophic $\alpha MHC^{719/+}$ mice with losartan for 2 weeks prior and during cyclosporine A induction of hypertrophy, which prevented the emergence of hypertrophy, nonmyocyte proliferation, and fibrosis.[57] Although the results of the animal studies are particularly encouraging for the prevention of fibrosis and for the demonstration of at least one of the pathways leading to the fibrotic phenotype, similar results have not been reproduced in clinical trials.[58,59]

Statin drugs are demonstrated to inhibit angiotensin II–mediated cardiac hypertrophy.[60,61] Senthil and associates, treating 15 prehypertrophic βMHC^{Q403} rabbits with atorvastatin 2.5 mg/kg/d versus a placebo group for 1 year showed prevention of hypertrophy development and a reduction

in both myocyte cross-sectional area and collagen volume fraction.[62] Although statins appeared to reverse hypertrophy and fibrosis and to prevent the development of the phenotype in HCM animal models, these results were not replicated in clinical trials in humans.[63,64] Possibly, as happens with angiotensin blockers, initiation of statin treatment after the establishment of overt hypertrophy may not be beneficial, stressing the potential utility of these drugs and their maximum effect when they are administered in the preclinical phase. Conclusively, there is no indisputable clinical evidence of the therapeutic effect of angiotensin II receptor inhibitors in HCM; as a result, their administration in everyday clinical practice is not indicated in HCM patients.

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Antifibrotic Agents

Spironolactone is a mineralocorticoid receptor blocker. In agreement with previous studies that pointed out the role of the renin-angiotensin-aldosterone system on cardiac remodeling in HCM, spironolactone appears also to be effective in modulating the pathogenesis of fibrosis in animal models.[65,66] However, long-term results in humans have not been documented. MacDonald and coworkers showed no beneficial effects on the hearts of cats with HCM, in addition to showing important side effects of long-term treatment (facial ulcerations).[67]

The rationale for using N-acetylcysteine in HCM comes from the demonstration of antifibrotic effects of the drug in several human tissues.[68,69] The potential benefit of this treatment in preventing fibrosis is well elucidated by preliminary results in two different animal models,[70,71] but there are no demonstrations of the efficacy of long-term treatment in humans yet.

Metabolic Modulators and Their Role in HCM

Perhexiline is a metabolic modulator that shifts myocardial substrate utilization from fatty acids to carbohydrates through inhibition of carnitin-palmitoyltransferase (CPT)-1 and, to a lesser extent, CPT-2.[72] Metabolic modulators are currently used in the treatment of ischemic heart disease. It is now evident that sarcomere mutations in HCM increase Ca^{2+} sensitivity, ATPase activity, and the energetic cost of mechanical contraction, thus leading to an impairment of diastolic LV relaxation and filling. Modulation of the metabolic pathway could improve the cycle of contraction-relaxation in hearts with HCM.[73] Encouraging results in nonobstructive HCM patients with exercise impairment, showing significant improvement in symptoms and exercise performance, highlight the possible important role of energy impairment in HCM as a primary phenotype, and stress the potential utility of perhexiline.[73]

Ranolazine is another factor that could possibly interrupt the abnormal intracellular calcium handling in preclinical HCM, deterring the establishment of an overt HCM phenotype by inhibiting late sodium channels. Transmembrane sodium fluxes and intracellular sodium concentrations are crucial in maintaining calcium homeostasis. Late sodium current (INaL) appears to be enhanced in hypertrophic cardiomyopathy, creating a pathophysiologic disturbance that leads to electrophysiologic and dynamic calcium abnormalities that may represent the underlying cause of the arrhythmogenesis and diastolic dysfunction. The drug is currently used as a metabolic modulator in ischemic heart disease, but further insights suggest the role of this drug as a selective inhibitor of INaL in cardiomyocytes.[74-77]

In this regard, ranolazine may ameliorate symptomatology by improving LV diastolic dysfunction in HCM. A phase 4 nonrandomized clinical trial is currently in progress evaluating the safety and efficacy of this drug in HCM patients with angina and dyspnea despite standard medical therapy. The study will measure the safety of ranolazine with regard to QT interval, adverse events, and drug tolerability, and its effect on angina, dyspnea, and quality of life.[78]

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The potential effects of eleclazine, another late sodium channel blocker in symptomatic HCM, are also currently being studied. Specifically, a large phase 2/3 randomized, placebo-controlled clinical trial is in progress evaluating the effects of the above regimen on exercise capacity in subjects with symptomatic disease.[79]

Conclusions

The currently applied medical intervention in HCM depends primarily on whether patients are symptomatic or not. Pharmacologic therapy is mainly used in patients with obstruction and appears to be effective; however, there is a group of individuals with symptomatology refractory to advanced medical treatment who

should be referred for septal reduction therapy. Unfortunately, there are very few options available for patients without LVOT obstruction but with severe symptoms.

It is important to note that current knowledge is derived primarily from observational studies and, therefore, any conclusions should be interpreted with caution. Of note, there have been only five randomized studies of medical therapies in HCM.[80] Translational research has resulted in a better understanding of the disease's pathophysiology, promoting the need for large-scale, randomized clinical studies that will standardize and advance current treatments in HCM. ■

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MAIN POINTS

- Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiac disease, with a prevalence of 0.2% in the general population. The disease is characterized clinically by unexplained left ventricular (LV) hypertrophy, and histologically by myocyte disarray, and interstitial and replacement fibrosis. Pharmacologic treatment in patients with HCM aims to control symptoms, to manage atrial fibrillation (AF) and ventricular arrhythmias, and to prevent thromboembolism and sudden cardiac death.
- β-Blockers are considered to be the first-line treatment, especially those agents that do not cause peripheral vasodilatation. In nonobstructive HCM, the beneficial effect of β-blockers is mainly mediated by the slowing of the heart rate and the prolongation of the LV diastolic period. The addition of disopyramide to a β-blocker is the optimal drug combination for obstructive HCM with symptoms refractory to β-blockers alone.
- AF is an arrhythmia closely linked to HCM, occurring in approximately 25% of patients, and constitutes a major determinant of symptoms, morbidity, and mortality. Maintaining sinus rhythm in symptomatic AF should be attempted either by pharmacologic means or electrical cardioversion.
- Late sodium current appears to be enhanced in hypertrophic cardiomyopathy, creating a pathophysiologic disturbance that leads to electrophysiologic and dynamic calcium abnormalities that may represent the underlying cause of the arrhythmogenesis and diastolic dysfunction. Ranolazine may ameliorate symptomatology by improving LV diastolic dysfunction in HCM.

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