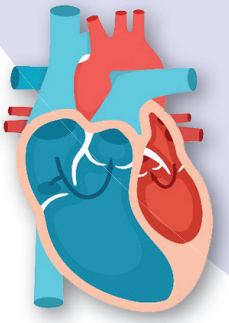


FOCUS ON HYPERTROPHIC CARDIOMYOPATHY

This resource provides general information about hypertrophic cardiomyopathy (HCM) and its nonpharmacological and pharmacological treatment.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a type of heart disease that is, in many ways, the opposite of what is thought of when the term cardiomyopathy is used. HCM is a genetically derived disease characterized by an overly thick (hence the term hypertrophic) left ventricle with generally normal ejection fraction.[1] Left ventricular outflow tract (LVOT) obstruction can, over time, produce systolic and diastolic dysfunction, but these are not often identified up front. As such, many patients can exhibit little or no symptoms initially and are only identified through screening programs (genetic or otherwise) or when a clinical event is experienced; some patients live to advanced age before symptoms appear or the disorder is inadvertently identified.

An estimated 750,000 individuals in the United States have HCM and up to 20 million worldwide when genetic studies are extrapolated to populations.[2] However, the lack of overtly apparent symptoms initially contributes to underdiagnosis of the disease. Only a little over 250,000 confirmed cases have been identified in the United States although the number has increased significantly over the past 10 years due to more emphasis on screening.[3] Underrepresented minority groups and women in particular are less likely to receive a diagnosis and referral for evaluation.[1]

Pathophysiology of HCM

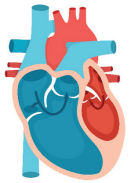
GENETIC FACTORS

HCM is a genetically inherited disease with an autosomal dominant pattern. At least 11 gene mutations have been identified as causative with even more having potential association, resulting in excess encoding of myofilaments or alterations in the proteins and building blocks constructing myocardium (i.e., the sarcomere).[4] The most common genetic mutations are in myosin-binding protein C (*MYBPC3*), beta-myosin heavy chain (*MYH7*), and cardiac troponin T or I (*TNNT2* and *TNNI3*, respectively).[5] *MYH7* mutations were the first genetic abnormality identified more than 30 years ago. While primarily a genetic mutation of the myocardium construction, associations also have been described with other genetically derived diseases affecting heart function and structure, such as Danon disease, amyloidosis, and Wolff-Parkinson-White syndrome, among others.[5]

OBSTRUCTIVE HCM

Obstructive HCM is primarily characterized by obstruction of the outflow of blood from the left ventricle into the aorta and will comprise the majority of patients with HCM over their lifetime (approximately 70%). This is caused by hypertrophy of the septal wall (the tissue separating the left from the right ventricle) causing the outflow tract to shift into the path of the mitral valve leaflets during systole, a process known as systolic anterior motion (SAM), creating an increased pressure gradient the ventricle must work against. SAM can be dynamic with day-to-day variability or increased in states of ventricular underfilling (e.g., dehydration, rising from sitting to standing), impacting symptoms. Patients with obstruction typically present with many of the symptoms typically experienced by patients with other types of heart failure, including exertional angina, shortness of breath (especially with exercise), fatigue, lightheadedness, and signs of extravascular volume. Symptoms can be present during rest but often are more pronounced or potentially only present during exercise, which increases the septal bowing into the outflow tract.

While obstructive heart failure is the most overt symptomatic association with HCM, these patients are also at substantial risk of sudden cardiac death due to ventricular arrhythmias as a result of the architectural abnormalities and associated disruption.[7] Atrial fibrillation is also commonly associated with HCM as a result of left atrial remodeling in response to chronically high pressures attributable to the outflow gradient. Sudden death is one of the hallmarks of the disease given symptoms and risk increase with heavy exertion. As such, HCM is one of the primary disorders leading to cardiac arrest in athletics and a major focus of screening athletes for cardiac risk.[8]



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NONOBSTRUCTIVE HCM

A smaller subset of patients with HCM will exhibit no or mild symptoms during the course of their lifetime. In general, these patients with no or minimal symptoms will have little life disruption and normal life expectancy.[9] The primary disease expression and major focus of treatment in these individuals is sudden cardiac death. Major risk factors associated with this include: family history of sudden death attributable to HCM, unexplained syncope, nonsustained ventricular tachycardia identified through cardiac monitoring, major left ventricular hypertrophy, apical aneurysm, extensive gadolinium uptake on magnetic resonance imaging (MRI), and left ventricular ejection fraction <50%.[7]

Importantly, patients with and without obstructive HCM can still develop systolic and diastolic dysfunction due to the anatomical changes.[1] These patients should be treated according to existing treatment paradigms for heart failure with reduced and preserved ejection fraction.

DIAGNOSIS AND SCREENING

Most patients with HCM have abnormal electrocardiogram (ECG) changes as a result of hypertrophied tissue, making this a generally effective approach in screening large populations.[8] Often, however, these changes are nonspecific and require further testing or may be potentially absent. Transthoracic echocardiography is the current standard to measure left ventricular wall thickness and assess the presence of any resting gradient and outflow tract obstruction.[1] Exercise or stress pharmacology (using positive inotropic drugs such as dobutamine) may be used to assess exercise-induced gradients. Otherwise, cardiac MRI (CMR) is rapidly also gaining traction as an enhanced imaging modality because of the association with contrast uptake and arrhythmia risk as well as greater resolution and specificity with respect to overall cardiac anatomy and function.[10]

On the subject of genetic screening, routine monitoring in the absence of ECG screening is not currently recommended.[11] Screening is recommended in first-degree relatives to a patient with HCM or another condition associated with HCM.

Nonpharmacological Treatment of HCM

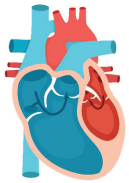
SEPTAL REDUCTION THERAPY

Despite the use of pharmacologic treatment to suppress LVOT obstruction, patients with obstructive HCM may continue to experience debilitating symptoms or have a gradient that is unresponsive to pharmacotherapy and require manual approaches to relieve outflow tract obstruction. The treatment of choice for septal reduction therapy is septal myectomy, which is an open-heart septal debulking surgery to restore normal LVOT gradients. The vast majority of patients receiving septal myectomy report improved quality of life with most becoming asymptomatic after surgery.[11] Operative mortality is low (<1%) when concentrated at higher-volume surgical centers.[1] However, patients who are diagnosed later in life and/or have higher operative risk or those who do not wish a major surgical procedure may be candidates for alcohol septal ablation as an alternative treatment.[12] This procedure is performed percutaneously via injection of concentrated ethanol into the septal coronary arteries, creating an infarct that causes reduced septal motion and wall thinning. The main complication of this procedure is approximately 10% of patients will require permanent pacemakers due to collateral infarction of the atrioventricular node, resulting in heart block.[13] Some patients will require repeat procedures, but most will report improved symptoms.

SUDDEN DEATH PREVENTION

While relief of symptoms in obstructive HCM is a strong focus of treatment, preventing the lethality in patients with either obstructive or nonobstructive HCM necessitates focusing on timely identification and termination of ventricular arrhythmias in at-risk patients through the use of an implantable cardioverter-defibrillator (ICD).[7] Major risk factors, including risk stratification, were discussed previously and risk-benefit evaluation should begin in adolescence (age >16 years). In a patient with no or minimal symptoms and no risk factors, ICD placement generally is not recommended.

Exercise moderation is also important to reduce the risk of sudden death.[11] Mild to moderate recreational exercise is generally recommended as safe for patients with HCM. Similarly, low-intensity competitive sports are thought to be reasonable for these patients. High-intensity competitive sports or recreation are higher risk and recommended to be the subject of shared decision making on an annual basis so the patient fully understands the risks and can be informed on an individual level. Certain sports authorities also may determine eligibility for participation on the basis of an HCM diagnosis. ICD placement solely for the facilitation of competitive sports is not recommended.[11]



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Pharmacological Treatment of HCM

BETA-BLOCKERS AND CALCIUM CHANNEL BLOCKERS

For patients with obstructive HCM, decreasing the impact of the outflow tract obstruction gradient is the main goal of therapy as long as the ejection fraction remains preserved. Relieving this gradient improves most patients' symptoms. Ironically, for a cardiomyopathy, drugs with negative inotropic properties are desirable in a patient with HCM. Beta-blockers were the first class of drugs investigated in HCM and are generally considered first-line due to their tolerability and widespread availability.[11] The choice of beta-blocker is not particularly important, but higher than usual doses may be required and some demonstrated evidence of adequate beta-blockade (e.g., reduced resting heart rate, reduction in obstruction on echocardiogram) is reasonable in addition to symptomatic reduction. Nondihydropyridine calcium channel blockers (diltiazem, verapamil) are an alternative first- or second-line agent in patients for whom beta-blocker therapy is either not tolerated or ineffective.[11] Combination therapy also may be considered with the caveat that additive risk of conduction-related disturbances causing bradycardia may be magnified as well as the anti-hypertensive effects of both classes.

ANTIARRHYTHMIC THERAPY

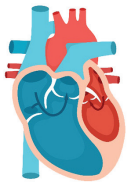
As discussed previously, patients with HCM are at risk for both ventricular and atrial arrhythmias and antiarrhythmic pharmacology may be employed to reduce symptomatic impact. Disopyramide, a Vaughan-Williams Class IA sodium channel blocker, has been of particular interest in the treatment of obstructive HCM because of its powerful negative inotropic properties. As such, disopyramide is recommended as an additive second- or third-line therapy in these patients who have refractory symptoms despite use of beta-blockers or calcium channel blockers, even those who do not experience arrhythmias.[11] Disopyramide unfortunately has strong anticholinergic properties for which some patients may require concomitant treatment with pyridostigmine and may also prolong the QT interval, placing some patients at risk for proarrhythmic effects. Other more traditional antiarrhythmic pharmacotherapy such as amiodarone or dofetilide may be used as an adjunct to other rhythm control modalities in patients with symptomatic atrial fibrillation unresponsive to rate slowing pharmacotherapy.

CARDIAC MYOSIN INHIBITORS

A new option, mavacamten, is the first direct cardiac myosin inhibitor; it selectively interferes with myosin activity thereby reducing left ventricular contraction, SAM, and outflow tract obstruction. Mavacamten was approved by the U.S. Food and Drug Administration in 2022 for the treatment of obstructive HCM and is currently available through specialty pharmacy distribution.

Mavacamten was investigated in the EXPLORER-HCM trial, which was a phase 3 double-blind, placebo-controlled study of mavacamten (starting dose 5 mg daily).[14] Patients were titrated up on mavacamten to a maximum of 15 mg daily (or given placebo) to target a resting LVOT gradient of <30 mm Hg. The primary endpoint of the trial was composite of a moderate increase in peak oxygen consumption during exercise with symptomatic improvement in New York Heart Association (NYHA) classification or a significant improvement in peak oxygen consumption with no worsening of NYHA class at week 30. The primary endpoint of the trial was reached in 37% of patients receiving mavacamten (n=123) compared with 17% of patients receiving placebo (n=128) (P <0.001). The mean reduction in LVOT gradient was -40 (SD ±40) in mavacamten-treated patients vs. -10 (SD ±30) in patients in the placebo group (P <0.001). In terms of safety, 7 patients treated with mavacamten had a reduction in ejection fraction to <50% with 5 requiring temporary drug discontinuation compared with 2 patients receiving placebo. As such, mavacamten approval was contingent upon a Risk Evaluation and Mitigation Strategy (REMS) program both for the potential development of systolic dysfunction as well as the potential for drug-drug interactions through its narrow therapeutic index in combination with elimination predominantly through cytochrome P450 (CYP) CYP2C19 and CYP3A4 metabolism (Table 1). Both providers and specialty pharmacies must be registered with the REMS program.

Mavacamten is also effective in reducing the need for procedural management of HCM in patients refractory to therapy. In the VALOR-HCM trial, patients with HCM receiving maximally tolerated first-line treatment and experiencing persistent symptoms were enrolled and randomized to mavacamten or placebo, titrating to LVOT reduction to a maximum of 15 mg daily.[15] At week 16, septal reduction therapy was recommended or guideline indicated in 17.9% of patients receiving mavacamten (n=56) compared with 76.8% of patients receiving placebo (n=56) (*P* <0.001).



FOCUS ON HYPERTROPHIC CARDIOMYOPATHY

Current guidelines have not incorporated mavacamten into existing treatment algorithms given the recent approval. However, it seems likely to become the preferred second-line therapy after beta-blockers or calcium blockers. Importantly, mavacamten may be used in combination with first-line treatments provided serial echocardiography assessing for systolic dysfunction is performed. However, mavacamten should not be used with disopyramide due to this risk. A second cardiac myosin inhibitor (aficamten) is in development and larger phase 3 trials are currently underway.

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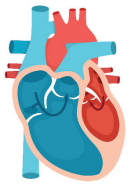


Table 1. Drug-Drug Interactions With Mavacamten and Suggested Management

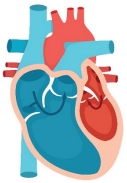
Drug Type	Impact	Examples	Suggested Management
Moderate to strong CYP2C19 inhibitors	Decrease mavacamten clearance	Cimetidine, esomeprazole, efavirenz, fluconazole, fluoxetine, fluvoxamine, modafinil, omeprazole, voriconazole	Avoid concomitant use
Strong CYP3A4 inhibitors	Decrease mavacamten clearance	Clarithromycin, HIV protease inhibitors, erythromycin, itraconazole, mifepristone, nefazodone, posaconazole, ketoconazole, ritonavir, voriconazole	Avoid concomitant use
Moderate to strong CYP2C19 inducers	Increase mavacamten clearance	Barbiturates, carbamazepine, phenytoin, primidone, rifampin, St. John's wort	Avoid concomitant use
Moderate to strong CYP3A4 inducers	Increase mavacamten clearance	Bosentan, carbamazepine, efavirenz, fosphenytoin, modafinil, nafcillin, phenobarbital, phenytoin, primidone, St. John's wort	Avoid concomitant use
Weak CYP2C19 inhibitors or moderate CYP3A4 inhibitors	Slightly decrease mavacamten clearance	Amiodarone, aprepitant, conivaptan, cyclosporine, diltiazem, dronedarone, fluconazole, fosamprenavir, grapefruit juice, imatinib, verapamil	Start therapy at no more than 5 mg daily In patients maintained on mavacamten, decrease dose by one level (e.g., change 10 mg daily to 5 mg daily) and increase monitoring; see labeling
Drugs with negative inotropic properties	Additive risk to cause ventricular systolic function	Disopyramide, beta-blockers, diltiazem, verapamil	Avoid disopyramide Monitor ejection fraction
Impact of Mavacamten on Other Medications			
CYP3A4, CYP2C9, CYP2C19 substrates	Increased clearance	Numerous – see approved drug label	May reduce effectiveness; monitor
Hormonal contraceptives	Increased clearance	Ethinyl estradiol, progestin	Use alternative contraceptive

Red = available over-the-counter in most community pharmacies.

Blue = non-pharmaceutical

CYP = cytochrome P450.

Source: Reference 16



FOCUS ON HYPERTROPHIC CARDIOMYOPATHY

ACKNOWLEDGMENTS

APhA gratefully acknowledges the financial support of Bristol Myers Squibb for the development of this resource. The following individual served as content advisor:

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Supported through an unrestricted grant from BMS.

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