# Medical Management of Hypertrophic Cardiomyopathy

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*Hypertrophic cardiomyopathy (HCM) is the most common genetically transmitted cardiomyopathy. The underlying cause of HCM has been attributed to a number of mutations within genes encoding primarily for sarcomeric proteins, which lead to a heterogenous phenotype of left ventricular hypertrophy in the absence of other causes (eg, hypertension, aortic stenosis, or a discrete membranous subaortic stenosis). Symptoms may range from mild to severely limiting and consist of dyspnea and chest pain with exertion or at rest, syncope, or even sudden cardiac death (SCD). The majority of patients with HCM are treated medically. The primary aim of therapy is to reduce symptoms, but it should also address the risk of SCD. Throughout the years, numerous medical treatments have been used to achieve symptom control in these patients, and include medications such as β-blockers, calcium channel blockers, amiodarone, disopyramide, and angiotensin receptor blockers. This review provides an overview of the current medical treatment of HCM.*

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**Key words:** Hypertrophic cardiomyopathy • Sudden cardiac death • β-Blockers • Calcium channel blockers • Disopyramide • Amiodarone • Angiotensin-receptor blockers

Hypertrophic cardiomyopathy (HCM) is the most common genetically transmitted cardiomyopathy. Present in 1 out of 500 individuals, it was originally described in 1869 based on pathologic postmortem specimens.[1-3] Brock[4] performed heart catheterization and intraoperative studies on a series of patients with HCM and described the left ventricular (LV) intracavitary gradients in these patients in 1957. In 1958, Teare described the necropsy finding

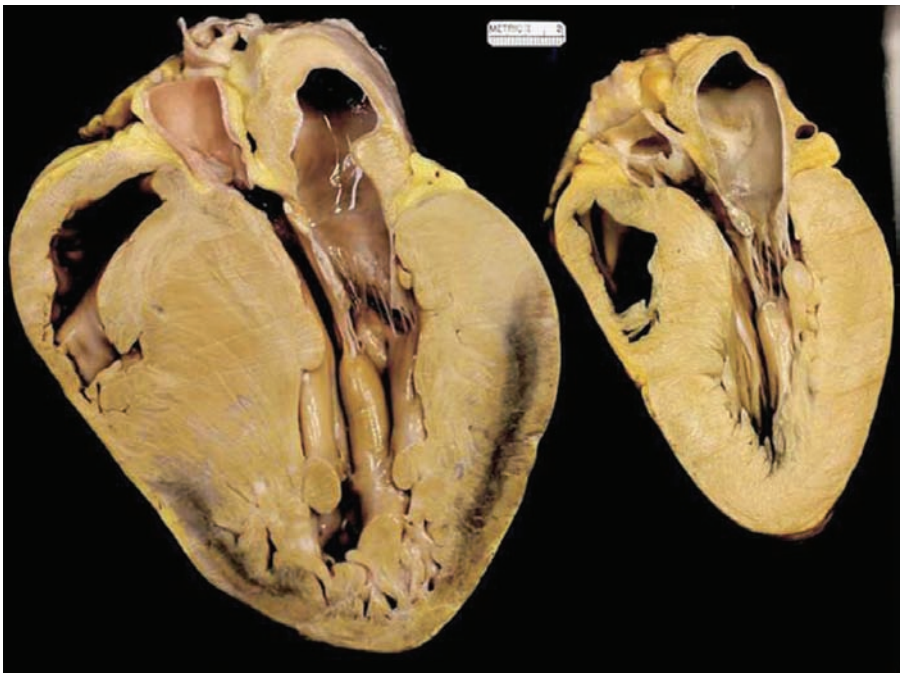

**Figure 1.** *Two heart necropsy specimens from teenagers with hypertrophic cardiomyopathy who had sudden death. Both specimens demonstrate left ventricular hypertrophy; there is asymmetric septal hypertrophy present in the specimen to the left and concentric hypertrophy in the specimen to the right. Reprinted from* Am J Cardiol. *Vol. 103, Roberts WC, Fifty years of hypertrophic cardiomyopathy, p. 431-434, © 2009, with permission from Elsevier.*

in 8 young adults with "asymmetric septal hypertrophy (ASH) of the heart."[5] Although often thought of as a disease of unusual septal thickness, multiple patterns of hypertrophy occur, including apical, concentric, or free wall distribution of hypertrophy. Figure 1 demonstrates the gross pathologic common findings from 2 patients with HCM. One patient had ASH and 1 patient had concentric left ventricular hypertrophy (LVH). HCM is defined by the World Health Organization as a heart muscle disease due to LVH without an apparent cause (eg, systemic hypertension, aortic stenosis, or a discrete membranous subaortic stenosis).[6,7] Generally, the hypertrophic features of this disease manifest during the accelerated growth phase of puberty. The hypertrophy usually remains stable following the onset of adulthood and is not generally related to the magnitude of LV outflow tract (LVOT) gradient or cavitary obliteration.

As shown in Figure 2, the underlying cause of HCM has been attributed to a number of mutations within genes encoding primarily for sarcomeric proteins.[8] The mutations as listed in Table 1 in implicated HCM may come from a defect in 1 of as many as 27 potential gene loci and is inherited in a Mendelian autosomal dominant pattern.[8] Among the most common mutations are those found in β-myosin heavy chain, troponin T, or cardiomyosin B. In addition to sarcomeric abnormalities, defects in calcium-handling and mitochondrial proteins have been implicated as potential sources for HCM. The genetic evaluation of individuals with a family history of HCM is important for addressing future risk and initiating early treatment. Fundamentally, this condition is one of sarcomeric dysfunction. In addition to the various mutations, there is marked heterogeneity in the phenotype of patients with HCM, in that is there is variability in the location and severity of LVH.[8-10]

On a microscopic level, HCM is characterized by myocyte disarray and cardiac fibrosis with collagen type I. The usual myocyte architecture is one of parallel sheets that allow for coordinated contraction as well as the conduction of electrical signals. In HCM a greater percentage of myocytes than normal are aligned in disorganized patterns, with cells positioned obliquely and even perpendicular to one another.[11-15] On electron microscopy, myofibril disarray is also present. Another feature of this condition is myocardial fibrosis, thought to be the major substrate for ischemia and arrhythmia contributing to the risk of sudden cardiac death (SCD) (Figure 3).[16-19] The myocyte disorganization and fibrosis leads to increased LV stiffness and impaired relaxation, resulting in elevated LV pressures, which contributes to symptoms of dyspnea.[20,21]

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The pathogenesis of HCM is incompletely understood. Sarcomeric dysfunction is obviously central to the development of pathology but the mechanism is uncertain. The disrupted sarcomere scaffold may lead to myocyte instability, causing them to develop in a bizarre fashion. Some theories include inappropriate ischemia and fibrosis secondary to sarcomeric inefficiency, whereas other theories identify an overresponsiveness to angiotensin and

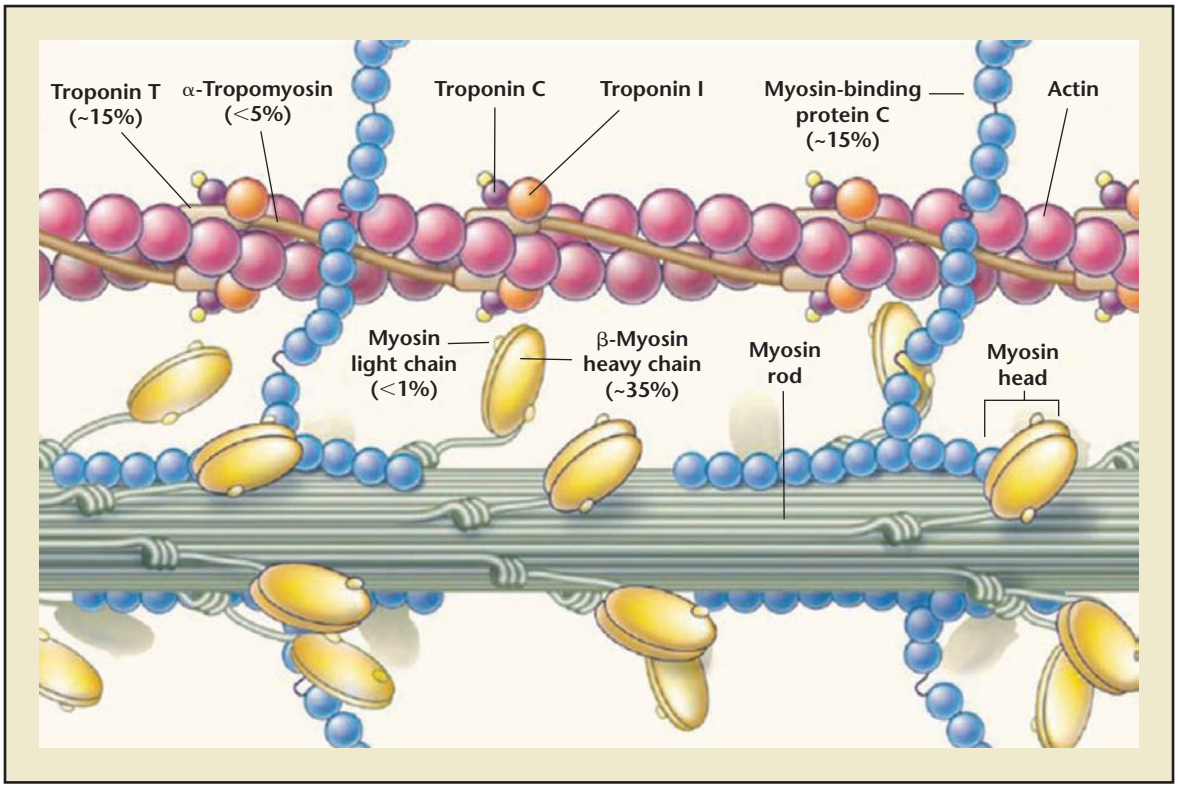


**Figure 2.** *This figure illustrates the various locations of potential sarcomeric mutations implicated in the pathogenesis of hypertrophic cardiomyopathy. Each site is labeled with a percentage that is representative of the relative occurrence of each mutation. Reprinted with permission from Spirito P et al.*[10s]

other neurohormonal factors causing hypertrophy and hyperplasia of intrinsic cardiac cells. The complexity of this disease is in part related to genotypic HCM having marked pleiotropy in phenotypic clinical expression. Not only are there multiple variations of hypertrophy, but separate individuals carrying the same mutation may develop differing anatomic and clinical features of HCM.[21]

Symptoms of HCM include shortness of breath, chest discomfort with exercise or at rest, palpitations, presyncope, syncope, and SCD, and are related to diastolic dysfunction, significant LVOT gradients, mitral regurgitation, and myocardial ischemia. Exertional dyspnea, as well as angina, or chest discomfort, are frequently worse after eating.[22-24]

HCM most commonly manifests during the adolescent growth period and has a variable clinical course. Some individuals may develop stable hypertrophy without symptoms, whereas others may develop severe disabling exertional and even resting dyspnea and chest pain.[4,21,25]

*The diagnosis of HCM is generally made by echocardiography. The echocardiographic hallmarks of HCM . . . include ASH with maximal LV wall thickness ≥ 15 mm, systolic anterior motion of the mitral valve, LV outflow gradient, and mitral regurgitation.*

The diagnosis of HCM is generally made by echocardiography. The echocardiographic hallmarks of HCM are shown in Figure 4 and include ASH with maximal LV wall thickness ≥ 15 mm, systolic anterior motion of the mitral valve, LV outflow gradient, and mitral regurgitation. Other associated findings often include right ventricular hypertrophy, diastolic dysfunction, aortic valve preclosure when there is an LVOT gradient, left atrial enlargement, and mitral annular calcification in older patients. It should be noted, however, that concentric hypertrophy is common. In a recent magnetic resonance imaging (MRI) study, it was found that 54% of patients had diffuse LVH involving 8 or more LV segments.[26] Resting LVOT gradients occur in up to 25% of patients.[26,27] As many as 50% of individuals may develop outflow tract gradients with physiologic maneuvers or pharmacotherapy.[28] In addition, the

Table 1
Summary of HCM Susceptibility Genes

| Gene | Locus | Protein | Frequency (%) |
|---|---|---|---|
| Myofilament HCM | | | |
| *TTN* | 2q24.3 | Titin | < 1 |
| *MYH7* | 14q11.2-q12 | β-Myosin heavy chain | 15-25 |
| *MYH6* | 14q11.2-q12 | α-Myosin heavy chain | < 1 |
| *MYL2* | 12q23-q24.3 | Ventricular regulatory myosin light chain | < 2 |
| *MYL3* | 3p21.2-p21.3 | Ventricular essential myosin light chain | < 1 |
| *MYBPC3* | 11p11.2 | Cardiac myosin-binding protein C | 15-25 |
| *TNNT2* | 1q32 | Cardiac troponin T | < 5 |
| *TNNI3* | 19p13.4 | Cardiac troponin I | < 5 |
| *TPM1* | 15q22.1 | α-Tropomyosin | < 5 |
| *ACTC* | 15q14 | α-Cardiac actin | < 1 |
| *TNNC1* | 3p21.3-p14.3 | Cardiac troponin C | < 1 |
| Z-Disc HCM | | | |
| *LBD3* | 10q22.2-q23.3 | LIM binding domain 3 (alias ZASP) | 1-5 |
| *CSRP3* | 11p15.1 | Muscle LIM protein | < 1 |
| *TCAP* | 17q12-q21.1 | Telethonin | < 1 |
| *VCL* | 10q22.1-q23 | Vinculin/metavinculin | < 1 |
| *ACTN2* | 1q42-q43 | α-Actinin 2 | < 1 |
| *MYOZ2* | 4q26-q27 | Myozenin 2 | < 1 |
| Calcium-Handling HCM | | | |
| *JPH2* | 20q12 | Junctophillin-2 | < 1 |
| *PLN* | 6q22.1 | Phospholamban | < 1 |

HCM, hypertrophic cardiomyopathy.
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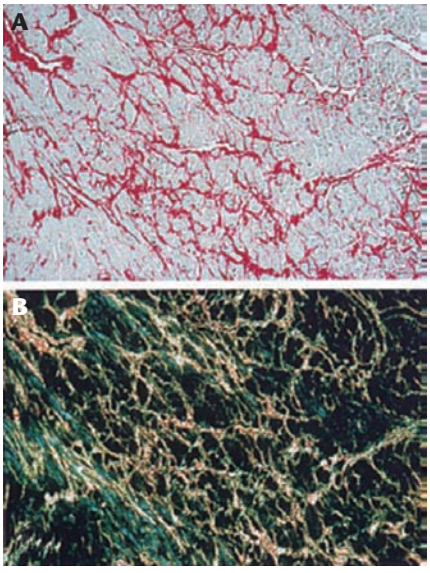


**Figure 3**. *Transversely cut cardiac muscle cells from a postmortem specimen taken from a 17-year-old patient with hypertrophic cardiomyopathy. The picrosirius red staining viewed by light **(A)** and **(B)** polarized microscopy demonstrate significant characteristic myocyte encasement within a dense network of collagen matrix. Reprinted from* J Am Coll Cardiol. *Vol. 35, Shirani J et al., Morphology and significance of the left ventricular collagen network in young patients with hypertrophic cardiomyopathy and sudden cardiac death, p. 36-44, © 2000, with permission from Elsevier.*

magnitude of the LVOT gradients often vary over time and with the patient's state of hydration and adrenergic tone. Invasive left ventriculography and computed tomography (CT) angiography also provide anatomic information for the diagnosis of HCM. Cardiac MRI can be added to echocardiographic data for both diagnosis and risk stratification of HCM (Figure 5).[29,30] MRI may be more precise for the measurement of LVH, as well as for the delineation of the precise site of LVH. In addition, delayed enhancement of gadolinium has been shown to identify those patients at increased risk of SCD. LVH or LV wall thickening resembling

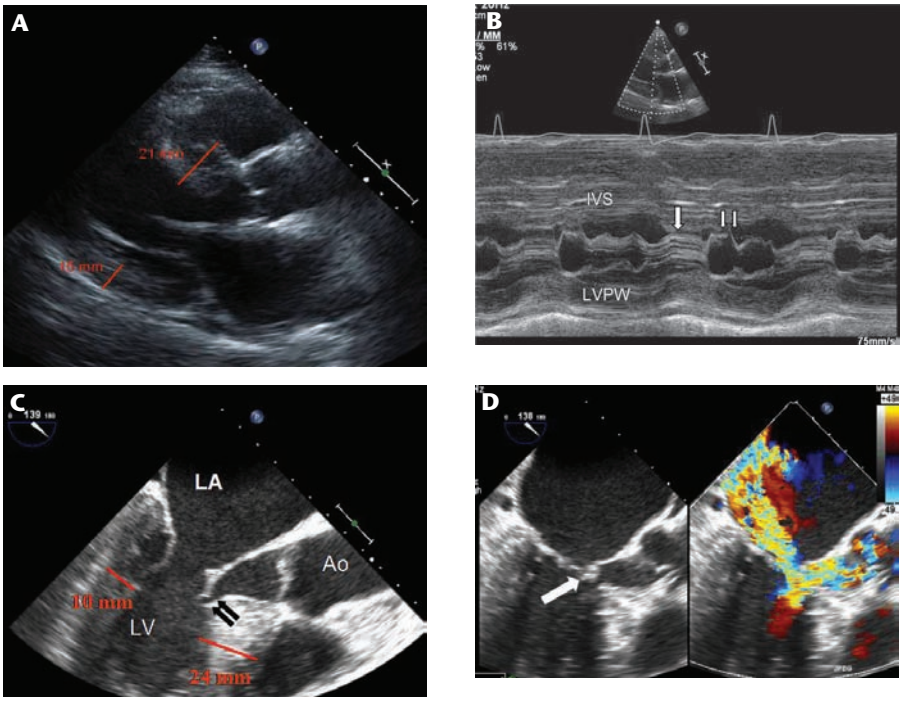


**Figure 4.** *Transthoracic and transesophogeal echocardiogram of a patient with hypertrophic cardiomyopathy.* ***(A)*** *Parasternal long-axis view of heart in diastole demonstrates asymmetric septal hypertrophy with the septum measuring 21 mm and the left ventricular posterior wall measuring 15 mm.* ***(B)*** *M-mode echocardiogram demonstrates a crowded left ventricle with systolic anterior motion (SAM) of the mitral valve* (arrow) *as well as diastolic apposition* (double arrow) *of the anterior mitral leaflet on the septum (IVS).* ***(C)*** *Transesophageal echocardiogram in diastole also shows asymmetric septal hypertrophy, dilated left atrium (LA), and septal plaque on the septum* (double arrow). ***(D)*** *Transesophageal echocardiogram in systole demonstrates systolic anterior motion of the mitral valve* (arrow) *and increased turbulence in the left ventricular outflow tract and concomitant posterolaterally directed mitral regurgitation. Ao, aorta; LV, left ventricle; LVPW, left ventricular posterior wall.*

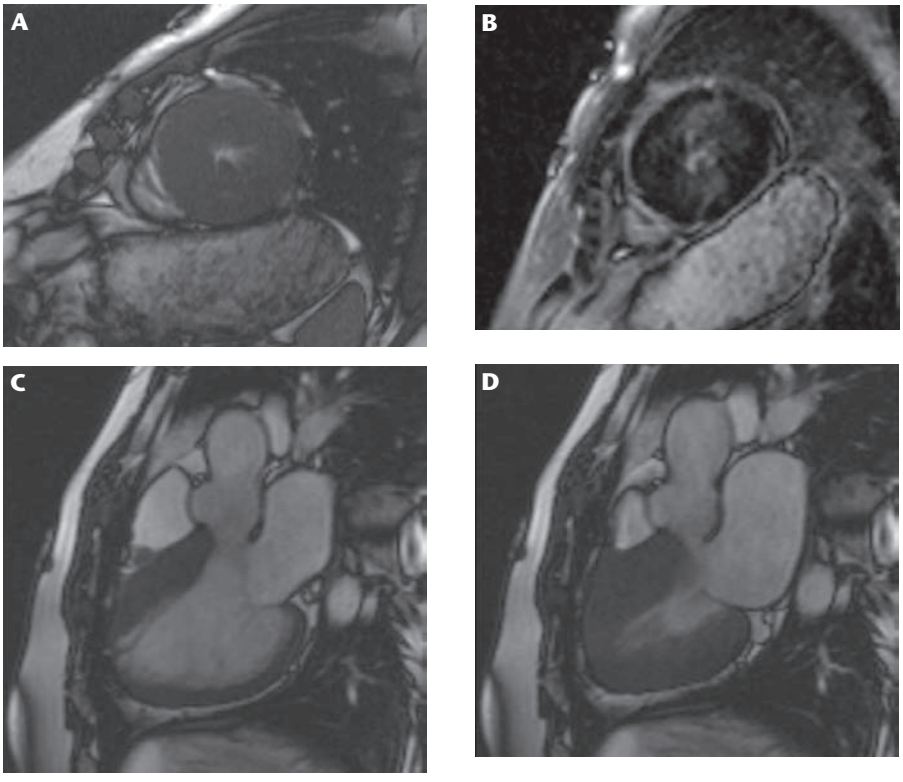


**Figure 5.** *Magnetic resonance image.* ***(A)*** *Short-axis cine image demonstrating near cavity obliteration in the same patient with hypertrophic cardiomyopathy.* ***(B)*** *Short-axis delayed enhancement image demonstrating enhancement in the mid myocardium, anteriorly and inferiorly, indicating presence of myocardial fibrosis.* ***(C)*** *Diastole.* ***(D)*** *Systole in a patient with left ventricular outflow tract hypertrophy. Image courtesy of Dr. Louise Thomson.*

HCM can also be seen in amyloidosis, Fabry disease, Noonan syndrome, Friedrich ataxia, mitochondrial cardiomyopathies, and (perhaps most commonly) severe systemic hypertension with or without chronic renal failure. In addition, it can sometimes be difficult to differentiate between athletic heart syndrome and HCM. The diagnosis of HCM can be confirmed by genetic testing; there are some patients who may have a normal cardiac mass yet be carriers for the mutation. In some cases, despite a normal LV mass, patients with high-risk genetic mutations are still at an increased risk for SCD.

The SCD risk may be further assessed with exercise stress testing and ambulatory 24- to 48-hour electrocardiographic monitoring.[4,28] As many as one-half to two-thirds of patients who do not have an LVOT gradient at rest develop a significant gradient on stress echocardiography.[27] Routine stress testing for patients with HCM has been shown to be safe and effective in evaluating exercise tolerance, functional capacity, the presence of an LVOT gradient, mitral regurgitation, exercise-induced pulmonary hypertension, and abnormal blood pressure response.[31] Failure of systolic blood pressure to elevate > 20 mm Hg during exercise and frequent episodes of nonsustained ventricular tachycardia (NSVT) on Holter monitoring are risk factors for SCD.[32-34] Evaluation for implantable cardiac pacemaker-defibrillator (ICD) placement includes the assessment of multiple risk factors. These risk factors include 1) prior cardiac arrest, 2) family history of SCD in a first-degree relative, 3) a high-risk genetic mutation, 4) unexplained nonneurogenic syncope, 5) frequent episodes of NSVT on Holter monitoring, 6) failure of systolic blood pressure to elevate > 20 mm Hg during exercise, and 7) LVH ≥ 30 mm in thickness. ICD placement for a single high-risk feature or a combination of several moderate risk factors should be considered on an individual patient basis. In 1 multicenter study conducted over 3 years, ICDs were shown to be effective in appropriately terminating ventricular arrhythmias in up to 25% of high-risk patients. Up to 5% of patients receiving ICDs for primary prevention and 11% of those treated for secondary prevention received appropriate shocks and cardioversion per year.[35] Of note, ICDs may remain dormant for up to 9 years before delivering appropriate life-saving cardioversion, highlighting the unpredictable nature of the SCD risk in HCM patients. In patients with a high risk for SCD and an ICD, low-dose amiodarone therapy has been used for prophylactic treatment of arrhythmia.[32,36,37]

β-blockers and calcium channel blockers (CCBs).[4,28] Despite medication use, there are many patients who still remain symptomatic. In addition, medical therapy has not been shown to change the risk of SCD in adults.[7] In symptomatic patients with high LVOT gradients (> 50 mm Hg), nonpharmacologic therapy including myectomy, dual-chamber pacing, and septal ablation have been advocated.[21,38]

Nonpharmacologic treatments are indicated in patients who, despite optimal medical management, have persistent significant symptoms (New York Heart Association [NYHA] class III/IV), resting LVOT gradient > 30 mm Hg, or exercise-induced gradients > 50 mm Hg.[28] Contraindications for alcohol septal ablation include septal thickness < 16 to 18 mm, significant mitral valve pathology, or left anterior descending artery stenosis. Septal myectomy is contraindicated in patients with septal thickness < 16 to 18 mm. The choice of surgical myectomy versus alcohol septal ablation should take into account the relative advantages and disadvantages of each intervention. Although alcohol septal ablation (a percutaneous catheter-based procedure) is less invasive than surgery, it often results in less immediate reduction in the LVOT gradient, and it may not completely treat the complex septal LVOT 3-dimensional anatomy. The procedural mortality ranges from 0% to 5%. Permanent pacemaker placement due to heart block, or ICD placement due to (or due to the concern for) the potential risk of

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The majority of patients with HCM are treated medically. Although the primary aim of therapy in HCM patients is to reduce symptoms, it should also address the risk of SCD. Some physicians also use the LVOT gradient and diastolic dysfunction to tailor their medical regimens. Several recent studies point to these physiologic assessments as predictive of long-term outcomes in patients with HCM, although others also point to the variability over time of these echocardiographic measurements.[38-41] The association and role of the resting LVOT gradient in SCD has been controversial. A recent study found the LVOT gradient to be insignificant as an independent risk factor for SCD; however, others have reported an association.[42] Traditional therapy for HCM symptoms includes

ventricular arrhythmias after alcohol septal ablation is not unusual. Repeat interventions due to persistent LVOT gradient and symptoms may also be warranted.[43] There have been reports of an increased risk of ventricular arrhythmias and even SCD after alcohol septal ablation.[44,45] Recent studies suggest that with newer myocardial contrast echocardiography techniques this risk may be minimized.[46] Surgical myectomy for LVOT gradient reduction requires thoracotomy and cardiopulmonary bypass, which extend the in-hospital recovery time up to 5 to 7 days. In addition, complications may include death, aortic regurgitation, ventricular septal defect, pacemaker dependence, residual gradient, and mitral regurgitation.[47] Myectomy has been evaluated longer than alcohol septal ablation as it has been performed for over 40 years. Long-term evaluation of surgical myectomy has shown a persistent reduction in resting and provocable LVOT gradients, as well as improvement in symptoms in more than 90% of patients treated. The periprocedural mortality risk at specified centers with expertise in surgical myectomy is reported to be 1% to 2%.[48,49] Similarly, alcohol septal ablation results in symptom improvement and a reduction in NYHA class, an increase in peak oxygen consumption and exercise time, and a drop in both resting and provoked LVOT gradients.[50-53] Thus, outcomes for both of these invasive procedures have shown similar significant improvements in both reduction of the LVOT gradient and symptoms. However, these procedures do not appear to reduce the risk of SCD.[54]

Recently, several alternative medications have been studied as possible adjuncts to therapy with promising results. This review provides an overview of the current medical treatment of HCM as well as the need for ongoing research in new therapeutic regimens.

## Medical Therapy

Pharmacologic treatment is the primary approach to treat symptoms of HCM (Table 2). Specific symptoms have been correlated with certain pathologic manifestations of the disease. Ultimately, however, LVH, the extent of myocardial fibrosis, and diastolic dysfunction are the main determinants of symptom status. Shortness of breath is often due to diastolic dysfunction caused by LVH, myocardial fibrosis, and myofibril disarray, resulting in a clinical picture of diastolic heart failure. However, in some patients, mitral regurgitation can be severe and contribute to dyspnea. Presyncope, syncope, and palpitations with exertion are often associated with impaired LV filling, LV outflow gradients, and LV cavity obliteration due to hypercontractility. Anginal chest pain is thought to be caused by relative coronary artery insufficiency in the presence of excessive myocardial mass, as seen in HCM. As shown in Figure 6, patients have also been found to have coronary arterial medial fibrosis and luminal narrowing of intramural coronary arteries. In addition, increased intramural pressure on the coronary vasculature and myocardial demand ischemia related to inefficient sarcomere coupling, as well as hypertrophy, may also exacerbate the flow–demand imbalance. The underlying goal of medical management is to improve diastolic function and reduce myocardial oxygen consumption and demand ischemia.[7]

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### *β-Blockers*

β-Blockers are generally the first-line therapy used in the treatment of HCM. Propranolol was the first drug in this class to be used, but has largely been replaced by metoprolol due to its better tolerability and more β-1 receptor selectivity.[7,10] On the other hand, carvedilol, although a β-blocker, should not be used due to its vasodilatory effect, which can increase both the LVOT gradient and mitral regurgitation.

β-Blockade addresses all 3 of the pathologic mechanisms of symptoms in HCM.[55] Diastolic function is enhanced by β-blockers that slow the heart rate, allowing for increased diastolic filling time of the left ventricle. By reducing the heart rate, β-blockers effectively relieve the inducible demand ischemia. A study on hemodynamics of HCM by Swanton and colleagues[56] demonstrated that patients treated with propranolol or practolol had a decrease in LV end-diastolic pressure (LVEDP) despite an increase in LV end-diastolic volume. Patients with HCM also have a marked increase in isovolumic relaxation, which has also been shown to improve with β-blocker therapy, with normalization to $< 50$ ms when patients are adequately treated.[57] This finding suggests that β-blockers may also affect diastolic function by increasing LV compliance. β-blockers are also suited for relief of anginal chest pain brought on by inefficient sarcomere function. In addition to relieving symptoms, high-dose β-blockers, when given to pediatric patients with HCM, have been noted in 1 series to decrease overall mortality.[58] By blocking catecholamine-induced

Table 2
Table of Pharmacologic Treatment Options for Hypertrophic Cardiomyopathy

| Drug Class | Mechanism of Action | Symptoms | LVOT | Diastolic Dysfxn | Coronary Artery | LVM | Mortality | SCD | Disadvantages/ Cautions |
|---|---|---|---|---|---|---|---|---|---|
| β-Blocker | Slows heart rate, increases diastolic time, negative inotrope | First-line treatment | Decreases exercise-induced LVOT gradient, no effect on resting gradient | Improves | Decreases demand ischemia by decreasing LV work | Decreases | ± | None | May worsen COPD/asthma medication side effects of depression, fatigue, bradycardia, impotence |
| Calcium Channel Blocker | Increases diastolic relaxation, coronary artery dilation, negative inotrope | Second-line, may use as first-line in patients with COPD/asthma | Can increase LVOT gradient | Improves | Decreases demand ischemia by decreasing LV work and causing coronary vasodilation | None | None | None | Caution in patients with LVOT gradient and elevated LV filling pressures |
| Amiodarone | Rhythm and rate control for atrial fibrillation; may also have mild β-blocker effects | Used for patients with concomitant atrial fibrillation | None | None | None | None | ± | ± | Long-term treatment may cause thyroid, liver, and pulmonary disease, as well as oto- and neurotoxicity |
| Disopyramide | Decreases heart rate, slows conduction through bundle of His, may propagate AV node conduction; blocks Na influx, Na-Ca counter-transport, thus indirectly decreasing intracellular calcium | Used in β-blocker refractory cases in addition to β-blocker; most useful in HCM with rest and exercise-induced gradients | Decreases LVOT gradient | Improves | Decreases demand ischemia by decreasing LV work and causing coronary vasodilation | None | None | None | May cause increase in AV conduction tachycardia; requires use in conjunction with β-blocker; side effects include dry mouth, prostatism, decreased systolic function, and narrow-angle glaucoma exacerbation |
| Angiotensin Receptor Blockers | Neurohormonal blockade of AT1 receptors | 33% of patients have noticed symptom decrease | Decreases rest and exercise gradient | Improves | None | Decreases | No studies | None | Growth retardation in children; decrease in blood pressure has potential to worsen LVOT gradients |

AT1, angiotensin-1 receptor, AV, atrioventricular; COPD, chronic obstructive pulmonary disease; SCD, sudden cardiac death; LVM, left ventricular mass; LVOT, left ventricular outflow tract.

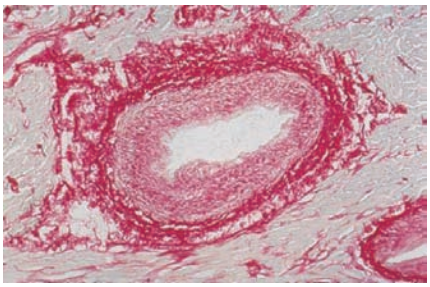

**Figure 6.** *Transverse section of an intramural coronary artery from the ventricular septum of a 28-year-old patient with hypertrophic cardiomyopathy using picrosirius red staining shows increased collagen in the thickened media as well as adventitial collagen and fibrosis. Reprinted from* J Am Coll Cardiol. *Vol. 35, Shirani J et al., Morphology and significance of the left ventricular collagen network in young patients with hypertrophic cardiomyopathy and sudden cardiac death, p. 36-44, © 2000, with permission from Elsevier.*

tachycardia, myocardial fibrosis is decreased, therefore decreasing the substrate for arrhythmias and diastolic dysfunction.[1,16-19,59]

β-Blockers were the first and are the most studied of the medical therapies in the treatment of HCM. The primary effect of these medications is symptom relief, although 1 study also points out a beneficial effect on overall survival if treatment is initiated in young adults.[58] However, treatment with β-blockers, especially in high doses, can lead to unwanted side effects (eg, severe bradycardia, impotence, fatigue, depression, dyspnea). Unfortunately, some patients may remain symptomatic despite optimal β-blockade therapy. In these cases, long-term management of HCM may require additional medical and nonmedical treatments.

*CCBs*

Many patients are refractory to or unable to tolerate β-blockers secondary to other comorbidities (chronic obstructive pulmonary disease [COPD], asthma), or become symptomatic over time while on these medications. The hypercontractile state in HCM is thought to be a result of increased calcium influx during systole, which also contributes to the LVOT gradient. Verapamil is the most commonly used of the CCBs for symptom management.[7] Although their mechanisms of action are different, as seen in Table 2, the final outcome is similar to that of β-blockade therapy.

CCBs act as negative inotropes to increase LV relaxation during diastole and slow contraction acceleration during systole.[7,55] A modest decrease in LVOT gradient, an increase in cardiac index, and an increase in exercise tolerance have been described in patients receiving verapamil.[60,61] Bonow and associates[60] identified by radionuclide angiography that the peak LV filling rate was similar between control subjects and HCM patients, but that there was a decreased contribution of LV filling during early diastole and an increased contribution during atrial systole (E:A reversal) in patients with HCM.[60] They further showed that this pattern of diastolic dysfunction seen in patients with HCM was ameliorated by treatment with verapamil and provided insight into the mechanism of CCB-enhanced LV filling.

Patients with HCM can have reversible myocardial perfusion defects related to underlying demand ischemia as well as intramural coronary artery medial thickening and endothelial dysfunction.[4] Verapamil reduces perfusion deficits in some patients with HCM.[62] Udelson and coworkers[63] and Taniguchi and associates[64] showed that exercise-induced reversible perfusion defects seen on $^{201}$Thallium single-photon emission CT imaging are significantly decreased, and in some cases eliminated, by the administration of verapamil.[63,64] Thus, use of verapamil correlates with the alleviation of anginal chest pain and may also reduce the development of myocardial fibrosis and SCD secondary to ischemic events.

These positive effects of verapamil on HCM must be balanced with its vasodilatory effects and its potential to decrease afterload in patients with severe LVOT gradients, which can cause a further increase in LVOT gradient, mitral regurgitation, and hypotension. Although verapamil has been shown to be effective for patients with refractory symptoms or those intolerant of β-blockers, its use is precluded in patients with significantly elevated LVEDP, because in this setting its use has been associated with the development of acute pulmonary edema and even death.[7]

*Disopyramide*

The medical treatment of patients with a single agent is not always completely effective. It is not uncommon for patients with severe LVH to be refractory to first-line treatment with β-blockers or calcium channel antagonists. In clinical trials performed in the 1980s and 1990s, disopyramide was found to reduce symptoms. Disopyramide is a class IA antiarrhythmic drug primarily considered a sodium channel blocker that also has CCB effects.[65] Numerous studies have shown disopyramide to be effective in improving symptoms and diastolic function. In addition, disopyramide reduces LVOT gradients, LV wall stress, and the severity of mitral regurgitation when the mitral regurgitation is related to systolic anterior motion of the mitral valve.[66-71]

Several studies have shown that LVOT gradients in HCM can be decreased, and in some cases abolished, by the administration of disopyramide. Pollick and colleagues[68] were the first investigators to show this in patients undergoing cardiac catheterization. They found that LV systolic pressure decreased following disopyramide administration and that aortic pressure actually increased, thus effectively reducing the LVOT gradient. The mechanism for LVOT reduction in these 35 patients was attributed to

the negative inotropic effect of disopyramide on a hypercontractile LV, as well as a secondary decrease in the magnitude of systolic anterior motion of the mitral valve.[66] Echocardiographic studies done by Duncan and associates[69] and Cokkinos and colleagues[72] showed a similar phenomenon. Duncan and associates[69] observed that the LVOT gradient and symptoms were completely abolished in children with obstructive HCM when treated with disopyramide. In the study conducted by Cokkinos and colleagues,[72] the combination of disopyramide and propranolol was compared with propranolol alone. In patients treated with a combination of both drugs, the LVOT gradient and NYHA class were significantly improved when compared with those patients treated solely with propanolol. This study was especially significant in that it offered the option of additional pharmacologic therapy in those patients who were refractory to β-blocker monotherapy. Sirak and Sherrid[73] described the utility and efficacy of disopyramide in the setting of COPD and contraindications to β-blockers. In a woman with HCM, a high LVOT gradient and severe COPD in the setting of pulmonary infection and respiratory compromise, intubation was avoided by the use of intravenous disopyramide. This intervention reduced the LVOT gradient from 92 mm Hg to 25 mm Hg and decreased the patient's respiratory distress to a level at which a complicating intubation became unnecessary.[73] Disopyramide, although similar in mechanism to CCBs, has a unique utility in that it may be added to β-blocker therapy and used effectively in patients with severe LVOT gradients, even in the presence of elevated filling pressures.

As a sodium channel blocker, disopyramide inhibits intracellular sodium entry and thereby effectively blunts the sodium-calcium exchange system, which decreases myocardial inotropy. This effect is similar to that seen with CCBs but without the same effect on systemic blood pressure.[65] Therefore, although inotropy is affected, there is not the potential for exacerbation of the LVOT gradient. Matsubara and associates[70] showed that, in patients with nonobstructive and obstructive HCM, disopyramide treatment resulted in a significant decrease in LV pressure decay and LV chamber stiffness. Sumimoto and colleagues,[71] using direct LV hemodynamic measurements at the time of cardiac catheterization, showed that disopyramide improved LV pressure-volume curves and consequently diastolic function.

In addition to improving diastolic function and the LVOT gradient, disopyramide can reduce the myocardial ischemia seen in HCM. A study performed by Niki and colleagues[74] evaluated the coronary flow and LV demand seen in patients with HCM who were treated with disopyramide. They observed that, although coronary blood flow did not change, the peak LV pressure and external work did significantly decrease, therefore leading to a decrease in the demand ischemia found in HCM. As such, disopyramide can alter not only hemodynamic symptoms of HCM but also the ischemic manifestations that contribute to the disease progression.

Disopyramide often offers significant benefit in patients who have failed to respond to either β-blockers or calcium channel antagonists. In an important multicenter study, Sherrid and coauthors[75] evaluated the use of disopyramide in patients who were refractory to or unable to tolerate β-blocker and CCB therapies. They evaluated 118 patients with HCM with resting LVOT gradients of $> 30$ mm Hg whose symptoms had not been controlled on monotherapy. Of these patients, 66% who were treated with disopyramide had symptomatic improvement and significant LVOT gradient reduction, from $75 \pm 33$ mm Hg to $40 \pm 32$ mm Hg ($P < .0001$). Moreover, they did not progress to needing nonpharmacologic intervention over a 3-year period. Of note, this multicenter analysis observed that the annual mortality risk of patients treated with disopyramide, a drug thought to be proarrhythmic, did not differ significantly when compared with similar patients who were effectively treated with monotherapy (1.4% vs 2.6%; $P = .07$). In addition, SCD in patients treated with disopyramide was not significantly different when compared with those treated with standard monotherapy (1.0% vs 1.4%; $P = .08$). Disopyramide therapy in this trial was associated with a trend toward a decrease in all-cause mortality and SCD.[75]

*In addition to improving diastolic function and the LVOT gradient, disopyramide can reduce the myocardial ischemia seen in HCM.*

The medical therapy of HCM patients can be problematic. β-blockers significantly reduce exercise LVOT gradients but are less effective in treating gradients found at rest. Additionally, their use in patients with concurrent reactive airway disease and their side-effect profile can hinder utility. CCBs, although effective for treating diastolic dysfunction and mild LVOT gradients, come with

the potential for worsening gradients and LVEDP in patients with moderate and severe disease. Disopyramide has been shown to be a safe and relatively well-tolerated medical treatment of obstructive and nonobstructive HCM when combined with β-blockers. Its utility has become more recognized and has proven to be an additional option in delaying the need for nonpharmacologic treatment of symptomatic patients. As with other medical therapies used for HCM, disopyramide does have several limitations. One limitation of disopyramide is the potential for severe anticholinergic side effects, including xerostomia, abdominal discomfort, nausea, constipation, and urinary retention.[76] These side effects can be mitigated by the use of slow-release pyridostigmine, an anticholinesterase medication, without the loss of efficacy.[77,78] Patients concomitantly on amiodarone or other QT interval-prolonging drugs should not be prescribed disopyramide due to the additive effect on QT interval prolongation and a risk of torsades de pointes. In addition, disopyramide has a risk of thrombocytosis and agranulocytosis, which should be regularly assessed.

*Amiodarone*

The natural history of HCM may include the development of increasing diastolic dysfunction, left atrial enlargement, and (in some) atrial flutter or fibrillation. These arrhythmias complicate the disease process as they worsen symptoms and include an increased risk of thromboembolic disease.[79] Amiodarone, a class III antiarrhythmic medication, has been used in treatment of rate and rhythm control of atrial arrhythmias in the general population. Its use for arrhythmia control in patients with HCM has been validated and is generally practiced.[1,80] In addition to providing rhythm control of these patients, amiodarone has β-blocking properties that allow for combined therapy in 1 medication.[36,81] Amiodarone is specifically able to address atrial arrhythmias, and can also be used for its negative inotropic effects.

Although symptom relief is paramount, one of the most feared complications of HCM is SCD. SCD may have multiple etiologies, including atrial and ventricular arrhythmias, bradyarrhythmias, diastolic dysfunction, systemic arterial hypotension, and myocardial ischemia.[82] In addition to the aberrant conduction caused by myocardial disarray, the fact that patients with HCM have a high likelihood of continued subendocardial ischemia puts them at risk for fibrosis and re-entrant ventricular tachyarrhythmias. Studies performed to date have yet to show clear benefit of medications in the prevention of SCD.[83] In particular, amiodarone has been evaluated extensively as it possesses antiarrhythmic properties that have been effective in treating other cardiac conditions.[84] Several studies performed by Fananapazir and colleagues[85] and Fananapazir and Epstein[86] have shown that although amiodarone may improve symptoms and atrial arrhythmias modestly, it may also increase SCD risk. In evaluating pre- and postamiodarone electrophysiologic studies in patients with HCM, it was observed that 20% of those treated with amiodarone developed delayed conduction in the atrioventricular, Hissian, and Purkinje systems. In addition, 50% of these patients had a lower threshold for inducible ventricular tachycardia.[86] In corroboration with these findings, several studies have shown that a substantial number of patients with HCM currently on amiodarone prophylaxis still have a high risk of SCD and appropriate ICD discharges.[35,87] Conversely, in 25 HCM patients with documented NSVT, McKenna and associates[37] showed that amiodarone was protective from SCD over a 2.6-year follow-up period. Another study performed by Cecchi and coworkers[32] risk stratified patients based on frequency of documented NSVT. Those with multiple repetitive episodes of NSVT were deemed high risk and treated with prophylactic low-dose amiodarone, which seemed to provide a protective effect from SCD. Although amiodarone possesses significant antiarrhythmic properties, its long-term use is somewhat negated by its side-effect profile, which includes pulmonary fibrosis, thyroid function abnormalities, and liver toxicity. The studies at present are inconclusive with regard to the use of amiodarone for treatment of ventricular tachycardia or the prevention of SCD. Although commonly used in patients with high risk for malignant arrhythmia, the efficacy of amiodarone with regard to SCD prophylaxis in patients with HCM remains questionable and possibly detrimental. Because of the limited number of patients studied, there are inadequate data to ascribe a detrimental or beneficial therapeutic effect of amiodarone on ventricular tachycardia and SCD in patients with HCM.

*Angiotensin Receptor Blockers*

Angiotensin receptor blockers (ARBs) are relatively new medications designed for the treatment of hypertension and heart failure. They act mainly on heart tissue angiotensin 1 receptors (AT1), but these receptors can be found throughout the vascular system, brain, and kidneys as well. ARBs have been successful in altering the progression of heart failure not only through the alleviation of hypertension but also by the blockade of neurohormonal signaling on the

heart itself.[88] Sadoshima and Izumo[89] were able to characterize the critical role which angiotensin II (Ang II) plays in the pathogenesis of heart failure. They showed that myocardiocytes in culture responded to Ang II by increasing protein synthesis and becoming hypertrophic. At the same time they identified that nonmyocardiocytes found within the heart tissue, mainly fibroblasts, responded to Ang II by increasing both protein synthesis and DNA synthesis representing hyperplasia. Furthermore, they found that treating these cultures with losartan, an AT1 receptor blocker, but not PD 123319, an angiotensin 2 receptor (AT2) blocker, protected the cells from undergoing the Ang II-induced changes.[89] This model for heart failure has been extrapolated to hypertrophic cardiomyopathy and Ang II has been thought to play a crucial role in the signaling pathway leading to increased myocardial fibrosis and myocyte disarray.[89,90] In addition, genetic analysis of patients with HCM have shown disease-modifying polymorphisms in the renin-angiotensin-aldosterone system, which affect the degree of LVH.[91]

Several recent studies have shown promise in the use of ARBs not only for symptom control, but also for halting and even reversing functional, pathologic, and molecular changes due to HCM. Araujo and associates[92] showed that patients with nonobstructive HCM (no resting LVOT gradients) and diastolic dysfunction treated with losartan for 1 year achieved a significant decrease in left atrial diameter, E/A ratio, pro-B-type natriuretic peptide (BNP) level, and symptoms when compared with those given a placebo. They found improvement of symptoms after medical therapy as well as improvement in LV diastolic function.

Another study, by Yamazaki and coauthors,[93] showed that losartan can halt the progressive LVH sometimes seen in HCM. In this study MRI was used to evaluate LV mass (LVM) before and after patients were given either losartan or placebo for 1 year. Posttreatment MRIs showed a slight decrease but insignificant change in LVM for the losartan-treated group, whereas the placebo-treated group had a significant increase in LVM. The final LVM to initial LVM ratio was significantly lower in the losartan-treated group as compared with the placebo-treated group.[93] Candesartan has also recently been shown to have a similar effect.[94] LVM has been shown to correlate positively both with symptoms of HCM and patient mortality.[95]

On a molecular level, ARBs also seem to suppress factors that lead to disease progression of HCM. Ang II exerts its neurohormonal effects through 2 receptors, AT1 and AT2. It has been shown that although AT1 increases hypertrophy, fibrosis, and hyperplasia, AT2 actually may act to counter these effects. The actions of these receptors are mediated through transforming growth factor-β (TFG-β), which, among other effects, stimulates the deposition of collagen α1. Angiotensin-converting enzyme inhibitors typically cause an overall decrease in the level of stimulatory Ang II, thus reducing the activity of both AT1 and AT2 receptors. This can have less of a beneficial effect, as both the profibrotic effects of AT1 and antifibrotic effects of AT2 are blunted simultaneously. ARBs such as losartan are more specific for the AT1 subtype and thus are better suited for the amelioration of neurohormonal-mediated disease.[89] Collagen α1 is the protein responsible for the majority of myocardial fibrosis seen in HCM and has been shown to correlate with early mortality. It is secreted into the blood as procollagen α1 and converted into its active form once in the cardiac tissue. Increased fibrosis is thought to be a substrate for SCD because postmortem and cardiac MRI studies have shown a correlation between the degree of fibrosis and the risk of SCD.[16-19] Thus, this feature of HCM represents an important prognostic factor in disease progression.[96] Kawano and colleagues[97] observed that, in patients taking valsartan, there was a significant reduction in the level of procollagen α1 when compared with those taking placebo. Also supporting this finding, Lim and coworkers[98] found that HCM transgenic mice treated with losartan had a significantly decreased level of collagen α1 as well as TGF-β when compared with placebo-treated mice. Their study further examined myocardial specimens that showed a significant decrease in cardiac fibrosis in mice treated with losartan when compared with the placebo-treated group. The losartan-treated mice actually achieved levels of cardiac fibrosis comparable with nontransgenic mice after 43 days of treatment, suggesting that this phenotypical expression of HCM may be a reversible phenomenon.[98]

*Several recent studies have shown promise in the use of angiotensin receptor blockers not only for symptom control, but also for halting and even reversing functional, pathologic, and molecular changes due to HCM.*

The neurohormonal signals of the angiotensin system have been implicated as a central element leading to heart failure progression. In recent trials using ARBs, HCM patients have responded favorably in terms of

symptoms as well as in molecular and functional studies. Biomarkers including TGF-β, BNP, procollagen α1, as well as myocardial fibrosis, diastolic dysfunction, and left atrial diameter, have been shown to improve in patients treated with ARBs. Studies using cardiac MRI to evaluate in vivo myocardial fibrosis have shown a correlation between these biomarkers as well as disease severity and adverse clinical outcomes.[30,99-102] Recent data have suggested that HCM patients with an increased left atrial volume, a marker for long-term untreated diastolic dysfunction, have a 10-fold increased risk for myocardial events.[103] In the past, medical therapy has focused on symptom control and not addressed the underlying pathology of the disease. ARBs may represent a new therapeutic approach in the medical treatment of both symptoms and underlying pathology of HCM.

## Medications to Avoid

In HCM, medications that result in either volume depletion (diuretics, nitrates), LV hypercontractility (digoxin, dobutamine, dopamine, milrinone, and other vasopressors with β-agonist characteristics), and afterload reduction (hydralazine, minoxidil, prazosin, nitroprusside, dihydropyridine CCBs, and angiotensin-converting enzyme inhibitors) should be avoided as they may result in LV underfilling, LV hypercontractility, and exacerbation of the LVOT gradient, mitral regurgitation, and a drop in forward cardiac output and hypotension. In addition, medications that promote tachycardia (albuterol, theophylline, and other β-agonists) should also be avoided as shortening of the diastolic filling period further compromises the already impaired diastolic function characteristic of HCM patients.

## Conclusions

HCM is a markedly heterogenous pathologic condition that may manifest clinically in many ways. In the assessment of these patients, the presence of severe hypertrophy, LVOT gradient, diastolic dysfunction, myocardial ischemia, and fibrosis can all be found in differing degrees and combinations. This makes medical management a challenge in that there is no standard regimen. Fortunately, as more research is conducted, we gain more understanding of the potential utility of each class of medication in this condition.

Each class of medication has unique abilities to alter physiologic and clinical sequelae of HCM (Table 2). The negative inotropic and chronotropic effects of β-blockers and CCBs allow for increased LV diastolic filling time and decreased exercise-induced LVOT gradient and myocardial ischemia. The addition of disopyramide to a β-blocker can have potential benefit in patients with LVOT gradients at rest and with severe diastolic dysfunction. The antiarrhythmic medication amiodarone has utility in treating HCM-related atrial fibrillation and, in addition, may provide benefits similar to β-blocker therapy. The use of amiodarone in prevention of SCD still remains controversial and should not be used for this goal alone. Finally, the recent study of ARBs in the treatment of HCM has led to the understanding that these medications may have a positive effect not only on symptomatic improvement but on the underlying pathologic substrate contributing to disease severity and clinical risk. These medications are not without side effects and these should be weighed carefully when choosing a therapeutic regimen.

HCM is a complex disease with marked morbidity and mortality when left untreated. Although the medical treatment of this condition has grown significantly in recent years, patients with severe disease may still be refractory and require invasive procedures to alter their symptoms. Ongoing and future research in this field is necessary and may provide for a more complete understanding of effective management strategies. ■

### Main Points

- Hypertrophic cardiomyopathy (HCM) is the most common genetically transmitted cardiomyopathy and has variable penetrance as well as phenotypic expression.
- Echocardiography proves to be the most often used modality for diagnosis and prognostication of HCM.
- Medical management aims to address symptoms associated with diastolic dysfunction, left ventricular outflow tract gradients, and myocardial ischemia.
- The mainstay of treatment includes β-blockers, calcium channel blockers, and disopyramide, which can affect both left ventricular diastology and contractility.
- Although initial results look promising, future studies are needed to further understand the utility of angiotensin receptor blockers in the management of this disease process.

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