

# Advancements in Treatment for Hypertrophic Cardiomyopathy: Key Considerations for Managed Care Professionals

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## HIGHLIGHTS

- › Hypertrophic Cardiomyopathy: Diagnosis and Therapeutic Options
- › Managed Care Considerations in Treatment of Hypertrophic Cardiomyopathy
- › CE Sample Posttest

# Advancements in Treatment for Hypertrophic Cardiomyopathy: Key Considerations for Managed Care Professionals

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## Intended Audience

Managed care payers, pharmacy directors, pharmacy benefit managers, specialty pharmacy directors, and any other pharmacist and/or healthcare professional interested in scientific advances in the treatment of hypertrophic cardiomyopathy.

## Activity Overview

Recent research into the unique pathophysiology in hypertrophic cardiomyopathy (HCM) has determined cellular mechanisms that initiate hypercontractility cause the heart muscle to become abnormally thick or enlarged, leading to progressive heart failure and reduced quality of life. There are many clinical manifestations of the disease that healthcare professionals should be able to identify, including its incidence across age cohorts and rate of mortality in certain presentations. As HCM is a genetic disease, indications for early genetic testing should be followed as later presentations have been misdiagnosed and are associated with more severe outcomes, such as sudden cardiac death. Current treatment for HCM consists of medications and surgical procedures reserved for specific presentations, but these do not address the underlying genetic defect. However, clinical trials are underway, with promising results for therapy options that do address the underlying pathology and contractile mechanism that would reduce hypercontractility in HCM. Managed care professionals should be prepared to consider the inclusion of these new therapy options in a disease state for which there are no current targeted therapies and complex hospital and post-discharge rehabilitation costs. This activity will examine their value to improve length and quality of life for people with HCM, as well as their role in mitigating other medical costs for these patients.

## Statement of Educational Need

Hypertrophic cardiomyopathy (HCM) is a genetic condition characterized by abnormally thick or enlarged cardiovascular musculature. With no specific treatments currently available to address its underlying pathology, patients experience poor quality of life and decreased physical function. Commonly, patients with HCM are diagnosed in adolescence through genetic testing, but a significant proportion of individuals with HCM remain undiagnosed until later in life when the disease has progressed; most often, older patients with undiagnosed HCM experience sudden cardiac death. Pharmacists need to be familiar with guideline-recommended pharmacotherapy staging options to manage symptoms of HCM and stabilize disease progression, with use

of low-cost, generically available agents. However, some classes of drugs can in fact worsen hemodynamics and outcomes for patients with HCM, making it imperative that pharmacists understand the risks and limitations of these agents. Nonpharmacologic treatment options include implantable cardioverter-defibrillators (ICDs), devices that have been shown to improve outcomes in patients with HCM who have survived a sudden cardiac event, but are not without their own risks and complications. It is necessary for managed care professionals to remain informed about ongoing clinical trial results and stay ahead of developments in HCM treatment, as existing recommendations will be updated upon approvals for these investigational disease-modifying drugs. Currently, the unmet need for preventive strategies in HCM has contributed to high medical costs and has placed increased burden on the healthcare system. Aside from hospitalizations for cardiac events in patients with a principal diagnosis of HCM, about 20% of patients require additional institutional care or rehabilitation after discharge. Until specific treatment approaches that address the underlying pathology of HCM enter the market, managed care professionals must review and incorporate established clinical pathways for management of HCM and promote genetic testing for early identification of HCM, as early interventions have shown to reduce severe outcomes, such as hospitalizations and sudden cardiac death. Continuing education on emerging agents in the treatment of HCM will prepare managed care professionals for future conversations about the inclusion of these therapies in the HCM treatment algorithm.

## Educational Objectives

Upon completion of this activity, participants will be able to:

- Analyze the pathophysiology, prevalence, risk factors, and incidence of hypertrophic cardiomyopathy (HCM).
- Examine recent updates to guideline recommendations of current treatments as well as updates on clinical studies on agents in development for HCM.
- Explore the clinical and economic burden of HCM and discuss disease management strategies to improve patient outcomes.

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## Advancements in Treatment for Hypertrophic Cardiomyopathy: Key Considerations for Managed Care Professionals

### OVERVIEW

Through this supplement to *The American Journal of Managed Care*<sup>®</sup>, managed care professionals will increase their knowledge of emerging targeted therapies in the therapeutic landscape of hypertrophic cardiomyopathy.

### TABLE OF CONTENTS

<b>Participating Faculty</b>	<b>S110</b>
<b>Reports</b>	
Hypertrophic Cardiomyopathy: Diagnosis and Therapeutic Options	<b>S111</b>
<i>Ty J. Gluckman, MD</i>	
Managed Care Considerations in Treatment of Hypertrophic Cardiomyopathy	<b>S118</b>
<i>Patty Taddei-Allen, PharmD, MBA, BCACP, BCGP</i>	
<b>CE Sample Posttest</b>	<b>S126</b>

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**FACULTY**

**Ty J. Gluckman, MD**

Medical Director  
Center for Cardiovascular Analytics,  
Research and Data Science (CARDS)  
Providence Heart Institute  
Portland, Oregon

**Patty Taddei-Allen, PharmD, MBA,  
BCACP, BCGP**

Vice President, Clinical Programs and Services  
WellDyne  
Lakeland, Florida

**MEDICAL WRITING & EDITORIAL SUPPORT**

**Brittany Hoffmann-Eubanks, PharmD, MBA**

Owner  
Banner Medical, LLC  
Frankfort, Illinois

**Lori Uildriks, PharmD, BCPS, BCGP**

Clinical Pharmacist/Clinical Instructor  
Department of Pharmacy Practice  
University of Illinois at Chicago College of Pharmacy  
Chicago, Illinois

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**Ty J. Gluckman, MD,** and **Patty Taddei-Allen, PharmD, MBA, BCACP, BCGP,** have no relevant financial relationships with commercial interests to disclose.

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# Hypertrophic Cardiomyopathy: Diagnosis and Therapeutic Options

Ty J. Gluckman, MD

## Introduction

Hypertrophic cardiomyopathy (HCM) is the most common monogenetic cardiovascular disorder.<sup>1</sup> It is observed globally and inherited in an autosomal dominant pattern. Despite being equally distributed by sex, men are diagnosed more frequently than women.<sup>2</sup> The prevalence of HCM depends on whether a patient has subclinical or overt disease, and varies by age, race, and ethnicity.<sup>3</sup> While the prevalence of asymptomatic HCM ranges between 1:200 and 1:500,<sup>4</sup> symptoms are noted in fewer than 1 of 3000.<sup>2,5</sup> This discrepancy helps to explain why only about 100,000 of the estimated 750,000 Americans with HCM have been diagnosed. Sadly, this diagnosis gap disproportionately affects women and underserved populations (particularly Blacks/African Americans).<sup>1,6</sup>

HCM was first reported in the early 1960s as idiopathic hypertrophic subaortic stenosis.<sup>7</sup> For decades that followed, various names were used to describe this condition.<sup>8</sup> Terms such as hypertrophic obstructive cardiomyopathy have proven confusing, as roughly one-third of patients do not develop left ventricular outflow tract obstruction. Preference has been given to the term HCM.<sup>2</sup>

Understanding of HCM has evolved significantly over the past 15 years, driven by greater appreciation of diagnostic features, genetic factors, and the disease's clinical course.<sup>9</sup> The purpose of this article is to review HCM's diagnosis and management.

## Etiology and Genetics

Genetic mutations involving one or more cardiac sarcomere, Z-disc, and calcium-controlling proteins underlie most cases of HCM.<sup>10-12</sup> To-date, more than 200 mutations involving 20 genes have been reported.<sup>13</sup> Most common among them are those involving beta myosin heavy chain 7 (*MYH7*) and myosin-binding protein C3 (*MYBPC3*), affecting about 70% of patients who are variant positive.<sup>2</sup>

While between 30% and 60% of individuals with HCM have an identifiable genetic variant, a significant number of individuals lack a known pathologic genotype or related family history.<sup>2,14</sup> Importantly, patients with HCM and a known sarcomeric mutation, such as *MYH7*, have a 3-fold greater risk of adverse outcomes compared with those without.<sup>15</sup> In addition, as many as 5% of

## ABSTRACT

Hypertrophic cardiomyopathy is an underdiagnosed genetic disorder, resulting from mutations in sarcomeric proteins. It has a highly variable clinical presentation, with some individuals remaining asymptomatic and others having significant limitation of functional status. The disorder is typically characterized by left ventricular hypertrophy that is not explained by another cause. Patients are further classified based on whether there is obstruction of the left ventricular outflow tract. To-date, there are no pharmacologic therapies that alter the natural history of the disease. Therapeutic approaches have instead focused on symptom relief and prevention of sudden cardiac death. Newer therapies under investigation represent potential means to improve limiting symptoms.

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For author information and disclosures, see end of text.

patients have 2 distinct pathogenic mutations and fewer than 1% have three.<sup>16,17</sup> Those with multiple mutations typically have more severe phenotypes that are more likely to manifest at an earlier age.<sup>13</sup>

Even among families with the same variant, age of onset and the timing of disease expression can be variable.<sup>2</sup> This phenotypic heterogeneity suggests that other factors beyond the sarcomere mutation itself likely play a role.<sup>2,8</sup> As an example, morphologic features (eg, mitral-valve enlargement and microvascular abnormalities) can vary in those with a given variant, suggesting that there may be contribution by other modifier genes or environmental factors.<sup>8</sup>

## Pathophysiology

The pathophysiology of HCM has multiple underlying drivers, including left ventricular outflow tract obstruction (LVOTO), mitral regurgitation, diastolic dysfunction, myocardial ischemia, arrhythmias, and autonomic dysfunction.<sup>2</sup> Depending on the patient, one of these may predominate or there may be a complex interplay between these contributors.<sup>2</sup> A majority of patients present with left ventricular hypertrophy (LVH) and myofibrillar disarray with fibrosis, which contribute to diastolic dysfunction.<sup>18</sup> Importantly, though, diastolic dysfunction may be secondary to a number of hemodynamic derangements (eg, prolonged and nonuniform ventricular relaxation, loss of ventricular suction, decreased chamber compliance, and abnormal uptake of intracellular calcium).<sup>18</sup>

LVOTO is typically present in approximately 75% of individuals with HCM and usually results from 2 primary mechanisms: (1) septal hypertrophy with narrowing of the left ventricular outflow tract (LVOT) and (2) anatomic alterations in the mitral valve apparatus.<sup>2</sup> Increased left ventricular pressure ensues, which may further exacerbate LVH, produce myocardial ischemia, and prolong ventricular relaxation. LVOTO is also associated with impaired stroke volume (SV) and increased risk of heart failure (HF), as well as decreased survival.<sup>19,20</sup> LVOTO in HCM, however, is extremely labile and can vary based on volume status, autonomic nervous system activity, pharmacotherapy, exercise, and physical positioning, even during a single diagnostic evaluation.<sup>21</sup>

In general, individuals with HCM, but without LVOTO (aka nonobstructive HCM), usually have a more favorable prognosis, with symptoms typically resulting from diastolic dysfunction.<sup>22,23</sup> There is the potential, though, for this and other types of HCM to “burn out,” transitioning to a dilated cardiomyopathy with a worse prognosis.<sup>18</sup>

## Clinical Course

Unlike many other cardiovascular disorders, HCM can appear at any life phase, from infancy to the seventh decade or later.<sup>13</sup> It is characterized predominantly by LVH in the absence of other cardiac, systemic, or metabolic disorders capable of producing similar hypertrophy, along with an identified or suspected pathogenic variant.<sup>2</sup>

The clinical course for those with HCM can be highly variable. For example, some patients lack symptoms, with little need for treatment; in contrast, others may exhibit a progressive course, requiring targeted treatment to improve morbidity and mortality.<sup>1,9,24</sup> Approximately 30% to 40% of those with HCM will experience adverse effects such as sudden cardiac death (SCD), progressive symptoms due to LVOTO or diastolic dysfunction, HF symptoms associated with systolic dysfunction, and/or atrial fibrillation (AF) with increased risk of thromboembolism.<sup>2</sup> Long-term studies have demonstrated significant benefit with conventional therapies and interventions, with a decrease in the annualized mortality rate to less than 1%, whether a patient has increased risk or develops one of these HCM-related complications.<sup>2</sup>

## Diagnosis and Prognosis

Evaluation for HCM may follow report of a positive family history, presence of clinical symptoms, incidental detection of a heart murmur, an abnormal electrocardiogram (ECG), or echocardiography for a different reason altogether.<sup>2</sup> Regardless of the prompting, if a clinical suspicion for HCM exists, patients should undergo evaluation with a comprehensive cardiac history (going back 3 family generations) and physical examination.<sup>2</sup> Classic physical exam findings include a systolic murmur, prominent apical point of maximal impulse, abnormal carotid pulse, and a fourth heart sound.<sup>2</sup> If LVH is suspected, individuals should also receive an ECG and cardiac imaging for diagnostic confirmation.<sup>2</sup>

In general, HCM is confirmed by the presence of increased left ventricular wall thickness (>15 mm up to 21-22 mm on average), most commonly by echocardiography.<sup>8</sup> More limited wall thickening (13-14 mm) can also be diagnostic when observed in those with an affected family member.<sup>2</sup> LVH is the hallmark of HCM and frequently is not concentric; rather, various asymmetrical patterns may be found.<sup>8</sup> If imaging by echocardiography is inconclusive, cardiovascular magnetic resonance (CMR) imaging is indicated. CMR can be helpful in many ways, including its ability to distinguish HCM from infiltrative or storage diseases and an athlete's heart.<sup>2</sup>

Some family members may have a positive genotype for HCM but are phenotype negative.<sup>8</sup> Importantly in these individuals, subclinical cardiac changes may still be found. These include ECG abnormalities, myocardial fibrosis, mitral leaflet elongation, diastolic dysfunction, and blood-filled myocardial crypts.<sup>8</sup>

Severity of LVH plays a significant role in HCM prognosis and risk of SCD.<sup>18</sup> In general, SCD with HCM is uncommon, with an annual event rate of 1%, but it does occur more often in younger as compared with older individuals.<sup>2</sup> It is also the most highly visible and devastating complication of HCM. SCD is thought to be due to ventricular arrhythmias resulting from autonomic overactivity secondary to LVOTO, microvascular ischemia, myocardial fibrosis, and myocyte disarray.<sup>25</sup> Multiple factors increase this risk further,

including left ventricular wall thickness  $\geq 30$  mm (so called “massive” hypertrophy) and a personal history of cardiac arrest, ventricular fibrillation, or sustained ventricular tachycardia (VT).<sup>18</sup>

There has been interest in identifying markers of SCD to help stratify implantable cardioverter defibrillator (ICD) use for primary prevention in HCM.<sup>2</sup> Because risk of SCD extends over one’s lifetime, it is recommended that it be reassessed every 1 to 2 years (Figure 1).<sup>1</sup> Tools to estimate risk are available; however, they may not account for newer risk markers including presence of systolic dysfunction, an apical aneurysm, and late gadolinium enhancement.<sup>26-28</sup> Risk stratification algorithms are also limited by low-positive-predictive values. As such, there is a growing need to leverage larger prospective HCM registries to better stratify risk, particularly in pediatric and non-White populations.<sup>2</sup>

Clinical judgment is required when assessing the prognostic strength of conventional SCD risk markers for individual patients.<sup>2</sup> Several major risk markers have been associated with increased risk of SCD.<sup>1,2,29</sup> Similarly, additional potential risk mediators have been identified that can inform the risk discussion. Based on current guideline recommendations, individuals with HCM and one or more major risk markers should be considered for ICD placement for primary prevention.<sup>2,18</sup> In addition, an ICD is recommended for anyone with a previous documented cardiac arrest or sustained VT.<sup>2,30,31</sup> An ICD is not recommended, however, solely for participation in competitive athletics.<sup>29,32</sup>

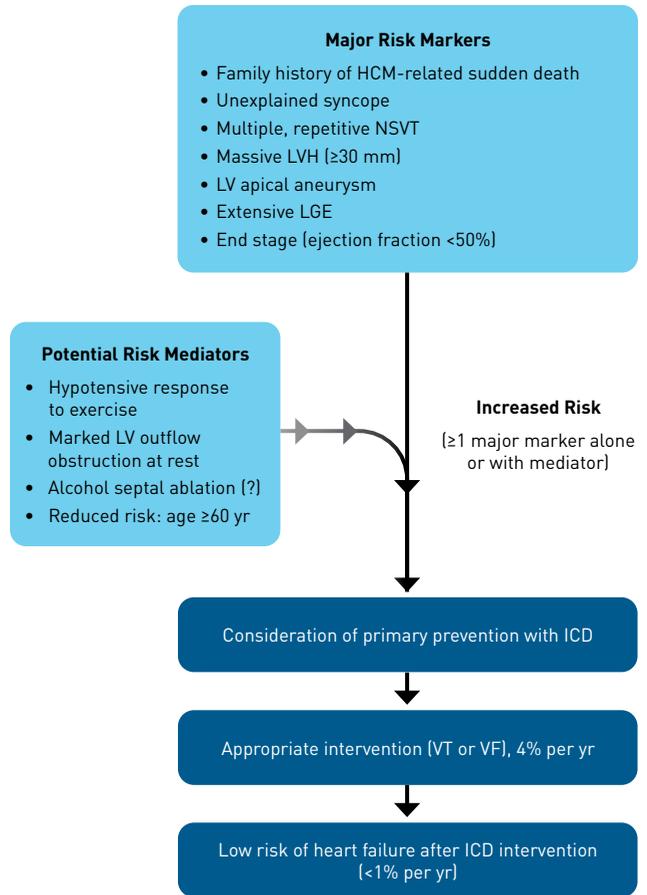
**Current Treatment Guidelines and Management**

The 2020 American Heart Association/American College of Cardiology (AHA/ACC) Guideline for the Diagnosis and Treatment of Patients with Hypertrophic Cardiomyopathy largely categorizes management decisions based on whether a patient’s HCM is obstructive or nonobstructive and whether AF, ventricular arrhythmias, and HF are present.<sup>2</sup> To this end, treatment must be individualized and requires a thorough understanding of the natural history of HCM. It is also important to remember that currently available pharmacologic therapy does not alter the natural history of HCM; instead, the primary goals involve relief of symptoms (eg, exertional dyspnea, palpitations, angina) and improvement in quality of life (QOL).<sup>13</sup>

**Obstructive HCM**

LVOTO in HCM can be quite labile. Nonetheless, treatment success is tightly tied to improvement in the patient’s LVOT gradient. It is critical that caution be exercised when introducing therapies for coexisting conditions that can cause or worsen LVOTO.<sup>2</sup> Diuretics, for example, decrease preload and can augment LVOTO. While they may be considered in asymptomatic patients or at low doses for patients with signs and symptoms of congestion, they can be highly problematic in those with symptomatic HCM. Beyond this,

**FIGURE 1.** Risk Stratification and Primary Prevention of SCD With ICDs in Patients With HCM<sup>1</sup>

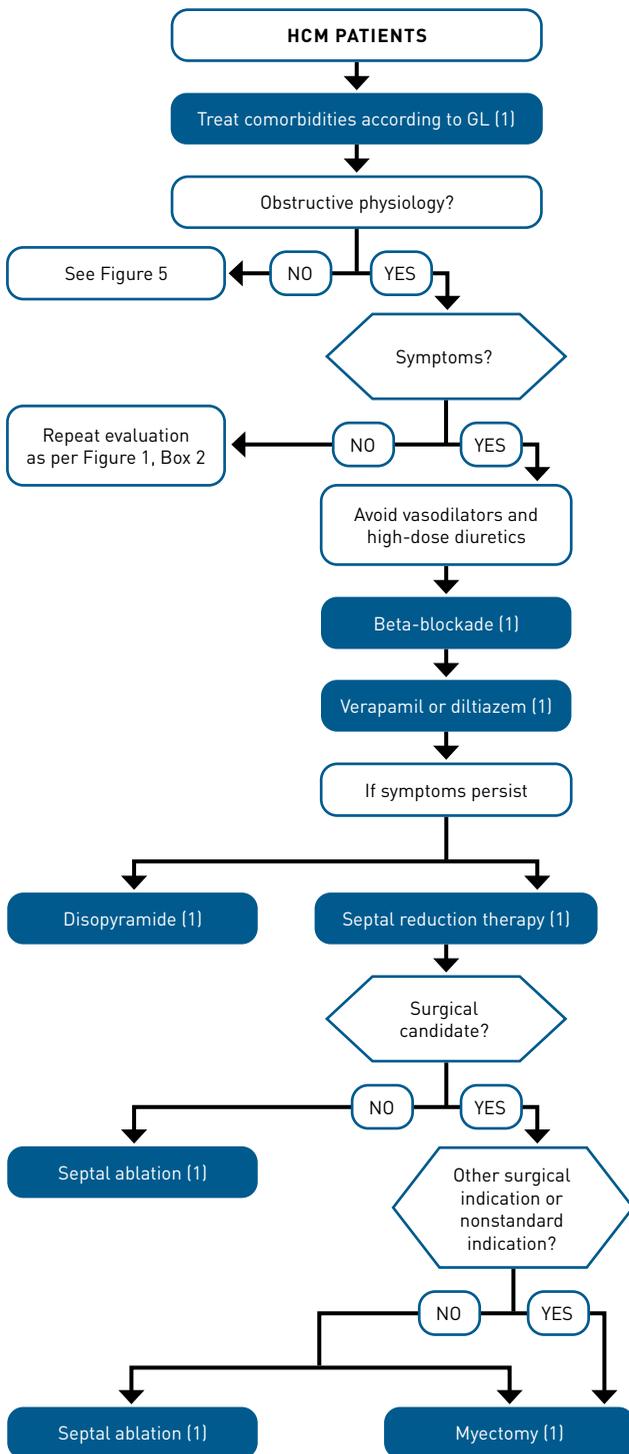


HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter defibrillator; LGE, late gadolinium enhancement; LV, left ventricular; LVH, left ventricular hypertrophy; NSVT, nonsustained ventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia.

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positive inotropic agents and pure vasodilators also have relative contraindication in symptomatic patients with obstructive HCM.<sup>2</sup>

Non-vasodilating  $\beta$ -blockers (eg, atenolol, propranolol) are usually utilized first line for symptom relief and should be titrated as tolerated (typically to a resting heart rate of 60 bpm) (Figure 2).<sup>2,13,33-35</sup>  $\beta$ -blockers are effective at improving exertional dyspnea and chest pain, largely by inhibiting sympathetic heart stimulation, decreasing oxygen consumption (through reduced heart rate, contractility, and myocardial stress during systole), and increasing diastolic filling.<sup>13</sup> Although  $\beta$ -blockers help to alleviate symptoms, they have not been shown to decrease the incidence of ventricular arrhythmias or SCD in HCM.<sup>26,36-38</sup>

**FIGURE 2.** AHA/ACC Algorithm for Management of HCM Symptoms<sup>2</sup>

Reprinted from *Journal of the American College of Cardiology*, Vol. 76 / No. 25, Ommen SR, Mital S, Burk MA, et al. "2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines," Pages e159-e240, © 2020, with permission from Elsevier.

Non-dihydropyridine calcium channel blockers (CCBs) [eg, verapamil and diltiazem] represent an alternative to  $\beta$ -blockers for symptom relief (Figure 2<sup>2</sup>). Because of their vasodilating<sup>39,40</sup> and afterload reducing effects, they should be used cautiously in patients with very high resting gradients (>80-100 mm Hg) and/or signs of congestive heart failure.<sup>2</sup> For those with significant obstruction and severe associated symptoms, it may be best to avoid CCBs altogether.<sup>2,39,41</sup> While combination therapy with  $\beta$ -blockers and CCBs for HCM is generally not recommended, this approach may be considered when used to manage concomitant hypertension.<sup>2,42,43</sup>

If patients with HCM fail to respond to  $\beta$ -blockers and non-dihydropyridine CCBs, advanced therapies such as disopyramide (a class 1a antiarrhythmic) and septal reduction therapy (SRT) may be considered. Although used infrequently as an antiarrhythmic, disopyramide is an important option in HCM due to its negative inotropic properties.<sup>2,39</sup> Because disopyramide can enhance conduction through the atrioventricular (AV) node and potentially facilitate rapid conduction with AF, it is important to use it in conjunction with AV nodal blocking agents such as  $\beta$ -blockers or non-dihydropyridine CCBs.<sup>2</sup> If patients experience limiting anticholinergic effects from disopyramide, pyridostigmine can be added to make it more tolerable.<sup>2</sup> In general, disopyramide is used for symptom relief and reserved for patients who fail first-line therapies and are not good SRT candidates.<sup>38,39,44</sup>

SRT is usually reserved for patients who fail to achieve symptom relief from guideline-directed medical therapy (GDMT) and continue to experience impaired QOL.<sup>2</sup> Because SRT performed in centers with limited experience addressing LVOTO is associated with increased morbidity, mortality, and need for mitral valve replacement, eligible patients should be referred to advanced HCM centers for evaluation and treatment.<sup>2,45-47</sup> In some patients, preference may be given to SRT over escalation of GDMT in follow-up to shared decision making. This is likely to be more common in patients with a low risk of procedural complications and a higher likelihood of medication-related adverse effects. Importantly, SRT is not recommended for patients with HCM who are asymptomatic, with a normal exercise capacity.<sup>2</sup>

Preference is given to surgical myectomy in patients with symptomatic obstructive HCM who have associated cardiac disease that requires surgical treatment.<sup>48,49</sup> Likewise, preference is given to alcohol septal ablation in patients with symptomatic obstructive HCM and contraindication to surgery, advanced age, or limiting comorbidities.<sup>45,50,51</sup>

### Nonobstructive HCM With Preserved Ejection Fraction

Diagnosis and treatment of nonobstructive HCM can prove particularly challenging given variability in disease onset, severity, and risk of adverse outcomes.<sup>15</sup> In spite of this, the risk of HCM-related

death appears to be no different from that with LVOTO. Similarly, dyspnea and chest pain are common symptoms in this population.<sup>2</sup>

Treatment of chest pain and dyspnea in those with nonobstructive HCM most commonly involves  $\beta$ -blockers and non-dihydropyridine CCBs. These agents help to slow heart rate, improve diastolic function, decrease left ventricular filling pressures, and reduce myocardial oxygen demand. Verapamil and diltiazem have also been shown to improve exercise capacity and stress myocardial perfusion defects.<sup>2,20</sup> Given that these agents have only been evaluated in very small trials, use largely reflects extrapolation from studies of patients with LVOTO.<sup>26,36</sup>

Loop and thiazide diuretics may be used to improve dyspnea and volume overload when congestion exists.<sup>2</sup> As with obstructive HCM, however, judicious use is recommended (ie, low-dose therapy or intermittent dosing) to mitigate the risk of symptomatic hypotension and hypovolemia.<sup>52,53</sup>

### HCM With Atrial Fibrillation

AF occurs in up to 20% of people with HCM, likely as a result of increased left ventricular end-diastolic pressure from LVOTO.<sup>2</sup> AF in the setting of HCM is associated with significant risks, including stroke and impaired QOL. Beyond therapies directed at symptom control, prevention of thromboembolism in this population is a priority. Unfortunately, traditional tools used to estimate stroke risk (eg, CHA<sub>2</sub>DS<sub>2</sub>-VASc score) fall short in patients with HCM and should not be used.<sup>2,13</sup>

An oral anticoagulant is recommended in all patients with HCM and AF, as thromboembolism occurs in up to 30%.<sup>1,26,36</sup> Similar to those without HCM, preference is given to a direct-acting oral anticoagulant (DOAC), with use of a vitamin K antagonist (VKA) second line. For those on a VKA, an international normalized ratio (INR) of 2 to 3 is sought.<sup>2,29</sup> For patients with subclinical AF (detected by an internal or external device), use of an oral anticoagulant for durations longer than 5 minutes but less than 24 hours is reasonable, informed by the duration of AF, the total AF burden, underlying risk factors, and bleeding risk. If an oral anticoagulant is to be used in this group, preference should be given to a DOAC first line.<sup>54</sup>

Restoration of sinus rhythm should be considered in those with AF, particularly in the presence of poorly tolerated symptoms. Options include antiarrhythmic drug (AAD) therapy (eg, amiodarone and sotalol), catheter ablation, and/or surgical ablation (particularly in those undergoing surgery).<sup>13,55,56</sup> In general, ablation is reserved for patients with inability to maintain sinus rhythm on AAD therapy or those in whom it is contraindicated.<sup>2</sup> Rate control usually involves a  $\beta$ -blocker, verapamil, or diltiazem, with therapy choice based on patient preference and comorbid conditions.<sup>36</sup>

### HCM With Ventricular Arrhythmias

Because ICD shocks are associated with worse outcomes and impaired QOL in HCM, prevention of VT is an important goal.<sup>2</sup> Most patients

who have concomitant HCM and VT are already on a  $\beta$ -blocker. Therefore, if VT persists or recurrent ICD shocks occur, AAD therapy should be initiated, with therapy choice based on age, underlying comorbidities, severity of disease, patient preference, and efficacy/safety.<sup>2</sup> If VT persists in spite of maximally tolerated AAD therapy, catheter ablation can be useful to reduce the arrhythmia burden.<sup>2</sup>

### HCM and Advanced HF

Left ventricular systolic dysfunction is uncommon in HCM ( $\approx$ 5%) and should invite a comprehensive evaluation for other potential causes such as coronary artery disease, valvular heart disease, and metabolic disorders.<sup>2,57</sup> Current guideline recommendations endorse use of GDMT in patients with HCM and a left ventricular ejection fraction under 50%.<sup>2</sup> In addition, it is reasonable to discontinue negative inotropic agents (eg, verapamil, diltiazem, or disopyramide) in this population. For those with nonobstructive HCM and advanced HF, it is reasonable to pursue evaluation for heart transplantation or mechanical circulatory support (ie, left ventricular assist device [LVAD]).<sup>20,26</sup> Finally, it is reasonable to pursue ICD placement or cardiac resynchronization therapy (CRT) in patients with HCM and a left ventricular ejection fraction under 50%.<sup>2,22</sup>

### Investigational Treatments

Presently, there are no disease-modifying nor preventive therapies for HCM. Treatments, such as valsartan, gene editing (CRISPR/Cas9), gene replacement therapy, and allele-specific silencing remain under investigation,<sup>2,58</sup> with uncertain efficacy and safety.<sup>2</sup>

### Mavacamten

Mavacamten is a first-in-class, small molecule selective inhibitor of cardiac myosin ATPase<sup>59</sup> that reduces actin-myosin cross-bridge formation.<sup>60,61</sup> It can improve the LVOT gradient and left ventricular filling<sup>61-63</sup> and was shown to significantly decrease post-exercise LVOT gradients in a small phase 2 trial (PIONEER-HCM) of patients with symptomatic obstructive HCM.<sup>64</sup> Individuals in this study who received mavacamten were also noted to have increased exercise capacity and improved New York Heart Association (NYHA) functional class.<sup>64</sup>

In follow-up to this, a phase 3, randomized, double-blind, placebo-controlled trial (EXPLORER-HCM) was initiated. Patients with symptomatic obstructive HCM were randomized 1:1 (n = 251) to receive once-daily oral mavacamten or placebo for 30 weeks.<sup>59</sup> The primary end point was a 1.5 mL/kg/min or greater increase in peak oxygen consumption (assessed by cardiopulmonary exercise test) and at least one NYHA class reduction or 3 mL/kg/min or greater oxygen consumption increase without NYHA class worsening. Treatment with mavacamten in this study was associated with a significant improvement in the primary efficacy end point (37% of patients treated with mavacamten vs 22% of patients treated

with placebo; 95% CI, 8.7-30.1;  $P = .0005$ ). There was also greater reduction in the post-exercise LVOT gradient ( $-36$  mm Hg; 95% CI,  $-43.2$  to  $-28.1$ ;  $P < .0001$ ), oxygen consumption ( $+1.4$  mL/kg per min;  $0.6$ - $2.1$ ;  $P = .0006$ ), and symptom scores (KCCQ-CSS  $+9.1$ ;  $5.5$ - $12.7$ ; HCMSQ-SoB,  $-1.8$ ,  $-2.4$  to  $-1.2$ ;  $P < .0001$ ). Finally, 34% more patients in the mavacamten group saw improvement by at least one NYHA class (95% CI,  $22.2$ - $45.4$ ;  $P < .0001$ ). Mavacamten was well tolerated, with a comparable safety profile to placebo. A single case of SCD was noted in the placebo group.<sup>59</sup>

Given mavacamten's ability to improve myocardial relaxation, it was also evaluated in a phase 2 double-blind, placebo-controlled, dose-ranging study of patients with nonobstructive HCM (MAVERICK-HCM).<sup>65</sup> This study enrolled symptomatic patients without LVOTO, with a left ventricular ejection fraction of 55% or above, and a N-terminal pro-B type natriuretic peptide (NT-proBNP) level greater than or equal to 300 pg/mL.<sup>65</sup> Participants were randomized 1:1:1 ( $n = 59$ ) to one of 2 doses of mavacamten (200 ng/mL or 500 ng/mL) or placebo, with stratification based on treatment with a  $\beta$ -blocker and cardiopulmonary exercise testing. Serious adverse effects were observed in 10% and 21% of those receiving mavacamten and placebo, respectively. Patients treated with mavacamten had a significant reduction in NT-proBNP (53%,  $P = .0005$ ) and cardiac troponin (34%,  $P = .009$ ) levels, indicating improvement in myocardial wall stress.<sup>65</sup> These results have set the stage for potential future investigation in nonobstructive HCM.

Recently, a phase 3 randomized, double-blind, placebo-controlled trial (VALOR-HCM) was initiated to assess the effect of mavacamten on reducing SRT procedures in patients with symptomatic obstructive HCM (NCT04349072).<sup>66</sup> The study will include approximately 100 participants and use a parallel group treatment. The primary outcome measure is the number of individuals who decide to continue with SRT before or at week 16 and the number of participants who remain guideline eligible for SRT at week 16.<sup>66</sup>

### CK-3773274 (CK-274)

Another investigational therapy, CK-274, is an oral cardiac myosin inhibitor under development for HCM.<sup>67</sup> This agent's mechanism of action is similar to mavacamten; however, its half-life is much shorter (12 hours for CK-274 compared with  $\approx 9$  days for mavacamten).<sup>68</sup> A phase 2, randomized, double-blind, placebo-controlled, dose-finding trial (REDWOOD-HCM) began in January 2020 (NCT04219826).<sup>67</sup> The purpose of the study is to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of CK-274. Due to the COVID-19 pandemic, the study was temporarily suspended.<sup>67</sup>

### Conclusions

In summary, while HCM is the most common monogenetic cardiovascular disorder, it remains widely underdiagnosed, with a large number of pathologic variants. It has a highly variable clinical

presentation, with some patients being asymptomatic and others having significant limitation of functional status. Diagnosis requires a thorough evaluation, including risk stratification for SCD. Treatment depends on symptom status, the presence of LVOTO, and coexistence of other cardiac conditions including AF, ventricular arrhythmias, and HF. While there are no approved disease-modifying therapies for HCM, it remains an area of ongoing investigation. ■

**Author affiliation:** Ty J. Gluckman, MD, is the Medical Director, Center for Cardiovascular Analytics, Research and Data Science (CARDS), Providence Heart Institute, Portland, OR.

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**Address correspondence to:** tyler.gluckman@providence.org

**Medical writing and editorial support provided by:** Brittany Hoffmann-Eubanks, PharmD, MBA

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# Hypertrophic Cardiomyopathy Considerations for the Managed Care Pharmacist

Patty Taddei-Allen, PharmD, MBA, BCACP, BCGP

## Introduction

Hypertrophic cardiomyopathy (HCM) is often seen in patients as an autosomal dominant genetic heart disease that equally affects men and women with a heterogeneous clinical course. However, women are not diagnosed as frequently as men. The prevalence of asymptomatic HCM in young adults is approximately 1:200 to 1:500 in the United States. In adults, the incidence of symptomatic HCM based on medical claims data is less than 1:3000 adults in the United States. However, the real burden is much greater when accounting for undiagnosed disease in the general population. Assessment of HCM may be precipitated by the appearance of symptoms, an abnormal electrocardiogram during a routine physical examination, a cardiac event, detection of a heart murmur, or cardiac imaging during family screening studies.<sup>1</sup>

HCM is a disorder characterized by left ventricular hypertrophy (LVH) not attributable to other cardiac, systemic, or metabolic causes with or without genetic evidence of a disease-causing sarcomere variant. A maximal end-diastolic wall thickness of 15 mm or greater anywhere in the left ventricle verified by imaging (cardiovascular magnetic resonance or 2D echocardiography) or 13-14 mm along with the presence of HCM in a family member or positive genetic test in the absence of other causes confirms a clinical diagnosis of HCM in adults.<sup>1</sup>

Approximately 30% to 60% of patients with HCM have a detectable pathogenic or likely pathogenic genetic variant. Variants in one of eight or more genes encoding cardiac sarcomere proteins or sarcomere-related structures cause the LVH of HCM. The 2 most common pathogenic sarcomeric gene variants are myosin-binding protein C3 (*MYBPC3*) and beta myosin heavy chain 7 (*MYH7*), present in 70% of variant-positive patients. Other genes (*ACTC1*, *MYL2*, *MYL3*, *TNNI3*, *TNNT2*, *TPM1*) each account for about 1% to 5% of patients. Although family members with a pathogenic variant will likely develop clinical HCM, there is variability of age of disease occurrence.<sup>1</sup>

## Clinical Burden

Although some patients with HCM may have an average life expectancy without debilitating symptoms or need for devices/surgery,

## ABSTRACT

Hypertrophic cardiomyopathy (HCM) is often seen in patients as an autosomal dominant genetic heart disease with a variable clinical course. It is characterized by left ventricular hypertrophy, and with some patients, there is no evidence of a genetic etiology or presence of HCM in family members. Young age at diagnosis and the presence of a pathogenic or likely pathogenic sarcomere variant predict greater lifelong risk for stroke, heart failure, ventricular arrhythmia, atrial fibrillation, or mortality. Most individuals affected with HCM live to an average lifespan due to improvements in earlier diagnosis, sudden cardiac death risk stratification, family screening, pharmacologic therapy, devices, and invasive septal reduction therapy. Although these interventions have improved mortality, they are associated with significant costs and morbidities. There are burdensome costs related to genetic testing, family screening, implantable cardioverter-defibrillators, alcohol septal ablation, septal myectomy, pacemaker placement, and cardiac transplantation. In addition to these economic considerations, patients with HCM may experience a diminished health-related quality of life. Shared decision making between the patient and physician, use of multidisciplinary teams at HCM centers, and judicious use of exercise when appropriate have been shown to improve patient outcomes. Currently, treatments for HCM do not treat the underlying illness. Although not yet approved by the FDA, cardiac myosin inhibitors have recently shown promise in clinical trials to treat the underlying pathology of HCM. If approved by the FDA, managed care pharmacists should be ready to assess their safety and efficacy to improve the clinical burden and quality of life of those affected by HCM and reduce medical costs for these patients against standard of care. Long-term safety and efficacy data showing reductions in hospitalizations, morbidity, and mortality will be needed to determine their actual utility in managing HCM and ultimate place in therapy.

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For author information and disclosures, see end of text.

other patients may experience a more severe disease course. Patients with a pathogenic sarcomeric gene variant or those diagnosed with HCM early in life may be at a greater lifelong risk for stroke, heart failure (HF), ventricular arrhythmia, atrial fibrillation (AF), or mortality. Approximately 30% to 40% of patients with HCM may experience HF symptoms associated with systolic dysfunction, AF with increased risk for thromboembolic stroke, progressive symptoms due to diastolic dysfunction or left ventricular outflow tract obstruction (LVOTO), or sudden cardiac death (SCD). Thirty percent of patients develop nonobstructive HCM (nHCM), while most patients develop obstructive HCM (oHCM) over time. HCM mortality rates have decreased to less than 1% per year with modern therapies, such as implantable cardiac defibrillators (ICDs) and alcohol septal ablation (ASA), and SCD risk-stratification strategies. Due to the decrease in SCD rates, HF is now the predominant cause of morbidity and mortality in patients with HCM.<sup>1</sup>

A study involving the international Sarcomeric Human Cardiomyopathy Registry provided additional insights into factors related to poorer outcomes. Patients with HCM aged 20 to 29 years and 50 to 69 years had a greater than 4 times and equal to or greater than 3 times mortality, respectively, than the general US population. A 77% (95% CI, 0.72-0.80) cumulative incidence of the overall composite outcome by 60 years occurred in patients younger than 40 years at diagnosis, compared with 32% (95% CI, 0.29-0.36) by age 70 years for patients diagnosed older than 60 years. The overall composite outcome was defined as the first occurrence of SCD, cardiac arrest, ICD implantation, cardiac transplantation (CT), left ventricular assist device (LVAD) implantation, New York Heart Association (NYHA) functional class III/IV symptoms, AF, stroke, and death. A pathogenic or likely pathogenic sarcomere genetic variant predicted greater than 2-fold increased risk for all outcomes, with the chance for ventricular arrhythmias being the highest (HR, 2.8; 95% CI, 2.1-3.9;  $P < .001$ ). AF and HF occurred most often, with the lifetime cumulative incidence of malignant ventricular arrhythmias occurring in 32% (95% CI, 0.23-0.40) in patients younger than 40 years at the age of diagnosis and in 1% (95% CI, 0.01-0.02) in patients older than 60 years.<sup>2</sup>

Currently, there is no cure for HCM. Although pharmacologic therapy, devices, and surgical management effectively prolong lifespan and treat symptomatology of HCM, substantial costs accompany these interventions.<sup>1,3-10</sup>

## High Costs of HCM

### Genetic testing

Evaluation of familial inheritance, including a 3-generation family history, is recommended by the HCM treatment guidelines as part of the initial assessment. Family history may be pertinent to the recommendation of subsequent genetic screening of the patient and at-risk family members. The clinical benefits of genetic testing in

HCM include confirmation of the diagnosis, cascade genetic testing in family members, and guidance regarding reproductive decisions. Cascade genetic testing in family members identifies the individual carrying the pathogenic variant requiring ongoing clinical surveillance while releasing those without from lifelong surveillance.<sup>1</sup>

The cost for genetic testing ranges from \$3000 to \$3800 for the first family member and \$250 for other family members if a mutation is identified.<sup>3</sup> Unfortunately, there is little consensus among medical payers in the United States on coverage for the genetic screening tests. In addition, different payers will include different panels for the same condition. Often, the medical policy, if it exists and is available to clinicians and patients, the requirement of "medical necessity" is often not determined until after a claim has been submitted.<sup>11</sup>

An Australian study investigating the cost-effectiveness of genetic and clinical screening compared with clinical screening alone concluded that the addition of genetic testing was a very cost-effective strategy with an incremental cost-effectiveness ratio of 587 Euro per quality-adjusted life-year (QALY) gained and 9509 Euro per additional life-year gained as determined by a probabilistic Markov decision model.<sup>12</sup>

### Hospitalizations

To evaluate the financial burden of oHCM on the healthcare system, a retrospective cohort study examined National In-patient Sample (NIS) records of 2605 patients admitted to the hospital with oHCM in the United States in 2013. Thirty-three percent of the patients included in the analysis were older than 64 years, 18% were younger than 45 years, and most were female (55%). The average stay was 4.9 days, with the majority (81.19%) of patients treated in urban teaching hospitals. The study defined hospital charges as the amount the hospital charged for the entire hospital stay, excluding professional fees. Researchers converted total charges to costs using cost-to-charge ratios based on hospital accounting reports from the Centers for Medicare & Medicaid Services (CMS). The mean and median cost of admission was \$25,433 and \$19,422, respectively. The actual mean and median hospital charges were \$88,646 and \$58,460, respectively. Comparatively, this was much higher than the reported 2014 US healthcare spending of \$9523 per person when the study was conducted. Private insurance paid for approximately 43% of the hospitalizations, Medicare for 37%, and Medicaid for 10%. The percentage of routine discharge was inversely proportional to age, declining from 90% to 65% from age 18 to 85. Most patients were discharged to home (76.39%), but a substantial remainder required further institutionalized care (13.05% home health care, 4.61% nursing home care, and 3.45% short-term hospital care).<sup>4</sup>

Another study specifically examined the impact of arrhythmias in patients with HCM on the cost of hospitalization and mortality.

Using NIS data of 225,816 hospitalizations of patients with HCM from 2003 to 2014, the study found a 10.5% relative increase ( $P < .001$ ) in the number of hospitalizations related to arrhythmias in patients with HCM, especially in patients with more comorbidities and aged 80 years or older. The total mean cost of care in patients with HCM and arrhythmia after adjusting for inflation rose from \$16,105 in 2003 to \$19,310 in 2014 ( $P$ -trend,  $< .001$ ), representing an absolute increment in annual national cost from \$125 million in 2013 to \$162 million in 2014 ( $P$ -trend,  $< .001$ ). The overall mean cost of HCM hospitalization with arrhythmia was \$20,522 versus \$15,636 with no arrhythmia, with ventricular fibrillation/flutter (VF/VFL) (\$39,108) and ventricular tachycardia (\$28,996). In patients with HCM and arrhythmias, in-hospital mortality was higher than those without arrhythmias. Still, there was a significant decrease in mortality rate in patients with HCM and arrhythmias from 6.2% in 2003 to 3.4% in 2014 ( $P$ -trend,  $< .001$ ). In patients with HCM and arrhythmias, the

mortality rate was highest in patients aged 80 years or older (7.4%), females (5.5%), and in Black (4.64%).<sup>5</sup>

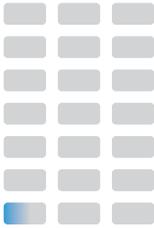
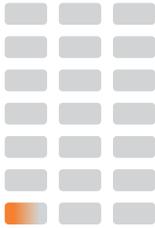
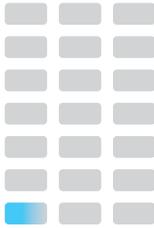
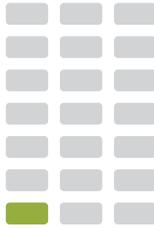
**Symptomatic treatment**

*Alcohol septal ablation (ASA) or septal myectomy (SM)*

Patients with HCM and symptomatic LVOTO refractory to medications may require invasive septal reduction therapy (SRT) with either ASA or SM. Each intervention is effective but has certain associated risks and benefits (Table<sup>1</sup>). Complete heart block as a result of SRT may require a permanent pacemaker in some patients post-procedure.<sup>1</sup> In 2014, the mean hospital charge in the United States associated with a pacemaker was \$83,521, with an in-hospital death rate of 1.46% and a mean length of hospital stay of 5.1 days.<sup>8</sup>

A study using the US National Readmission Database compared resource utilization, in-hospital mortality, and complication rates between the 2 age groups of patients with HCM undergoing ASA or

**TABLE.** Invasive Septal Reduction Therapies Outcomes<sup>1</sup>

	 <b>≤1%</b>	 <b>≤3%</b>	 <b>≤5%</b>	 <b>≤10%</b>	 <b>&gt;90%</b>
<b>Myectomy</b>	<ul style="list-style-type: none"> <li>• 30-day mortality</li> </ul>	<ul style="list-style-type: none"> <li>• Repeat procedure rate</li> </ul>	<ul style="list-style-type: none"> <li>• 30-day complete heart block requiring permanent pacemaker</li> <li>• Mitral valve replacement within 1 year</li> <li>• Greater than moderate residual mitral regurgitation</li> </ul>	<ul style="list-style-type: none"> <li>• 30-day complications (infection, major bleeding, tamponade, left anterior descending coronary artery dissection)</li> </ul>	<ul style="list-style-type: none"> <li>• Improvement ≥ NYHA class</li> <li>• Rest and provoked LVOT gradient &lt;50 mm Hg</li> </ul>
<b>Alcohol Septal Ablation</b>	<ul style="list-style-type: none"> <li>• 30-day mortality</li> </ul>		<ul style="list-style-type: none"> <li>• Greater than moderate residual mitral regurgitation</li> </ul>	<ul style="list-style-type: none"> <li>• 30-day complete heart block requiring permanent pacemaker</li> <li>• Repeat procedure rate</li> </ul>	<ul style="list-style-type: none"> <li>• Improvement ≥ NYHA class</li> <li>• Rest and provoked LVOT gradient &lt;50 mm Hg</li> </ul>

NYHA, New York Heart Association; LVOT, left ventricular outflow tract.

Adapted from Ommen SR, Mital S, Burke MA, et al. 2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on clinical practice guidelines. *J Am Coll Cardiol.* 2020;76(25):3022-3055.

SM. A total of 2245 patients with HCM underwent ASA (1272 patients  $\leq 65$  years, 973 patients  $> 65$  years) and 2113 patients SM (1739 patients  $\leq 65$  years, 374 patients  $> 65$  years) from 2010 to 2015. The median length of hospital stay was significantly longer (SM, 6 days vs ASA, 3 days;  $P < .001$ ) in both age groups, and the total median hospital costs were greater ( $\leq 65$  years: SM, \$28,459 vs ASA, \$13,847;  $P < .001$ ;  $> 65$  years: SM, \$32,429 vs ASA, \$15,343;  $P < .001$ ) in both age groups receiving SM versus ASA. The in-hospital mortality in patients undergoing SM was significantly greater in both age groups compared with patients undergoing ASA ( $\leq 65$  years: SM, 1.5% vs ASA, 0.3%; OR, 6.2; 95% CI, 1.01-38.00;  $P = .048$ ) ( $> 65$  years: SM, 6.7% vs ASA, 1.7%; OR, 4.29; 95% CI, 1.03-17.9;  $P = .046$ ).<sup>6</sup>

Although the initial resource utilization and costs were lower with ASA than SM, post-procedural healthcare utilization and costs associated with ASA may increase over time compared with SM. Another study examined claims data from the OptumLabs Data Warehouse of adult patients with oHCM from 2006 to 2018, comparing the 2-year cumulative post-procedural costs and healthcare utilization after SM and ASA. A total of 379 patients underwent SM and 185 ASA, with 53% being male and of the mean age of 56.3. There was a statistically insignificant increase in the 2-year mean number of physician office visits (20 SM vs 23.4 ASA) or emergency department visits (IRR, 1.16; 95% CI, 0.76-1.77) in patients undergoing ASA versus SM. The 2-year risk of hospital readmission was similar between the 2 groups (36.9% following SM and 43.8% following ASA). There was a nonsignificant increase in readmissions in the ASA group versus the SM group (IRR 1.54; 95% CI, 0.99-2.40). The median cumulative 2-year post-procedural costs were higher in those receiving ASA (\$22,165 [range, \$8848-\$81,143]) versus SM (\$20,170 [range, \$10,006-\$44,755]). Rehospitalization accounted for approximately 20% (for ASA) and 17% (for SM) of these post-procedural costs.<sup>7</sup>

#### *Implantable Cardiac Defibrillator and Short Atrioventricular Delay Pacing*

An ICD has proven efficacy in aborting potentially life-threatening ventricular tachyarrhythmias and preventing SCD in patients with HCM. HCM guidelines recommend using ICD as primary prevention based on risk factors and secondary prevention in individuals surviving a cardiac arrest or hemodynamically significant ventricular fibrillation/ventricular tachycardia.<sup>1</sup> An ICD system can deliver anti-tachycardia pacing, bradycardia pacing, cardioversion, and can be combined with cardiac resynchronization therapy when advised.<sup>9</sup> The mean hospital charges in the United States in 2014 for an implantable defibrillator were \$171,476, with an in-hospital death rate of 0.69% and a mean length of stay of 6.3 days.<sup>8</sup>

A Swedish study simulated the cost-effectiveness of an ICD over 12 years in terms of costs per life saved and cost per gained QALY versus treatment without an ICD in adults with HCM. The

mean age of ICD implantation was 51.8 years based on data from a nationwide HCM cohort. The assumed willingness-to-pay for a gained QALY was 53,050 Euro. The number of lives saved was 402 of the 1000 simulated patients after 12 years, and 2.5 patients needed to be treated during the 12 years to save one life. The cost per life saved is approximately 57,117 Euro, and the incremental cost for a gained QALY was 15,150 Euro. From the societal perspective, including effects on productivity losses, in terms of QALYs, ICD treatment was superior and less expensive.<sup>9</sup>

Short atrioventricular delay-pacing is a treatment alternative to SRT for the treatment of LVOTO in oHCM. The long-term-hemodynamic results associated with short atrioventricular delay-pacing are not inferior to myectomy, but no long-term randomized studies comparing it with SRT in comparable patient groups exist. A Swedish case-control study compared the outcomes of 31 pairs of patients with oHCM treated with myectomy or pacing from 2002 to 2013. Both treatments resulted in significant improvements in LVOT-gradients as well as NYHA class. The mean cost of hospitalization was significantly less for pacing than myectomy: 74,000 ( $\approx$ \$11,111 in 2013 USD)  $\pm$  16,000 ( $\approx$ \$2,402 in 2013 USD) Swedish krona (SEK) for pacing and 310,000 ( $\approx$ \$46,546 in 2013 USD)  $\pm$  180,000 ( $\approx$ \$27,027 in 2013 USD) SEK for myectomy,  $P < .001$ , with a significantly shorter in-hospital stay (2 days vs 7 days). The myectomy group had significantly more peri-procedural complications than the pacing group (35.5% vs 3.2%, respectively;  $P < .0001$ ). A pacemaker was implanted in 9.7% of patients peri-operatively and in 25.8% in late-follow up in the myectomy group. Freedom from re-interventions was observed in 61.3% in the myectomy group versus 90.3% in the pacing group ( $P = .003$ )<sup>10,13</sup>

#### *Cardiac Transplantation (CT)/Ventricular Assist Devices (VADs)*

A specific subset of patients with HCM may experience severe refractory congestive HF that ultimately requires CT. About 3.5% of patients may progress to a burnt-out end-stage distinguished by fibrotic replacement and chamber remodeling, causing systolic dysfunction and restrictive ventricular filling with a mean 3-year survival time. A heart transplantation is a life-saving intervention in patients with end-stage HCM. It is the only option to restore functional status and longevity among HCM patients with advanced HF.<sup>14</sup> However, CT is very costly and has associated risks and morbidities. The mean hospital charges in the United States in 2014 for CT were \$808,770, with an in-hospital death rate of 7.84% and mean length of stay of 45.4 days.<sup>8</sup> Heart transplantation also requires the lifetime use of immunosuppressant medications. About 10% of heart transplant recipients need renal replacement therapy or transplant due to calcineurin inhibitor-induced nephrotoxicity. Right HF and biventricular failure may occur early postoperatively. Heart transplant recipients may also experience rejection

and infectious complications. Coronary vasculopathy, requiring re-transplantation, develops in about 30% to 40% of heart transplant recipients within 5 years. Malignancy post-transplantation accounts for 10% to 23% deaths post-transplantation.<sup>14</sup> A study of evaluating outcomes in 535 adult HCM patients in the United States registered in the Scientific Registry of Transplant recipients with HCM awaiting a heart transplant between April 2008 and October 2016 determined the waitlist mortality was 9.6%. The 12-month heart transplant rate was 64.8%, and post-transplant survival in patients with HCM was 91.6% at one year and 82.5% at 5 years.<sup>15</sup> Bridge to transplantation (BTT) with an implantable VAD may be used in patients with HCM, but is difficult because of placement challenges due to small left ventricular chamber size, the presence of LVH (mid and distal left ventricular), and left ventricular muscle bundles, which could impede proper functioning. By report, VAD placement in patients with HCM may increase susceptibility to right ventricular dysfunction and hypotension. Many patients with HCM may not qualify for VAD placement, which may place them at a lower priority on the transplant list.<sup>14</sup>

### Health-related Quality of Life (HRQOL)

In addition to the economic costs accompanying treatment interventions for HCM, reduced HRQOL in patients living with HCM has been demonstrated in studies. The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a self-administered validated questionnaire measuring the perceived burden of HF symptoms. Scores range from 0 to 100, with higher values representing better HRQOL. A study in 91 patients with HF and HCM evaluated the HRQOL (57% males; median age 58) and found an overall moderate HRQOL impairment (median global KCCQ score, 67). NYHA class and the median global KCCQ score were inversely correlated (Kendall's tau b coefficient  $r = -0.33$ ;  $P = .001$ ). There were also significantly worse HRQOL scores in patients with pulmonary hypertension (resting pulmonary artery systolic pressure  $\geq 45$  mm Hg) than those without (median KCCQ score, 56.2 vs 77.5;  $P = .013$ ). Patients with a worse HRQOL score were older and had more severe functional impairment. These included a history of syncope, poor renal function, echocardiographic parameters of increased severity and/or dysfunction, and elevated pulmonary artery systolic pressure. The study identified estimated glomerular filtration rate and NYHA functional class as independent predictive factors of the HRQOL score.<sup>16</sup>

A study conducted between 2015 and 2018 used a conceptual model to capture patients' perspectives on the symptoms of HCM they were experiencing and their impact on their lives. A total of 444 participants who responded to the 80-question web survey reported symptoms of fatigue (74%), shortness of breath upon exertion (73%), lightheadedness (70%), exercise intolerance (57%), palpitations (54%), dizziness after exertion (54%), chest pain (39%), and syncope (24%). The impact of physical activity upon symptoms

varied, with the majority reporting slight (42%) or marked limitation (31%) of activity, and 6% reported being unable to be physically active without discomfort per survey. Eighty-four percent of patients with oHCM reported 4 or more symptoms compared with 55% of patients with nHCM. The majority of patients (70%) experienced symptoms somewhat or significantly worsening since diagnosis, having a more significant impact on their ability to work. The most commonly reported effects of HCM elicited during the concept elicitation interviews of 27 patients included emotional impacts (78%), restrictions of physical activities (78%), feelings of depression and anxiety (78%), and limitations on work (63%).<sup>17</sup>

HRQOL has also been shown to be impacted in patients with HCM and an ICD in a Swedish study. The study used a validated self-reported questionnaire (36-item short form). It analyzed the responses of 245 patients with HCM and an ICD, comparing responses with a Swedish age- and sex-matched control group. The physical functioning, role physical, general health, vitality, social functioning, role emotional, mental health, physical component summary, and mental component summary scores were significantly lower ( $P < .001$ ) than control (Figure 1<sup>18</sup>). The most considerable impact occurred in the general health domain, with a more significant effect seen in the physical component summary scores than the mental component summary scores. Subgroup analyses showed that AF or HF significantly impacted physical functioning, physical role, and general health. AF also had a significant impact on social functioning scores. Inappropriate ICD shock negatively impacted mental health while appropriate ICD therapy trended oppositely. The HRQOL was similar between primary and secondary prevention.<sup>18</sup>

### Improving Patient Outcomes

Crucial to improving patient outcomes is shared decision making. Adherence to recommendations can be enhanced when there is patient involvement in the treatment decision-making process. There should be a dialogue between patients and their healthcare providers informing them of the available testing and treatment options, including discussing all the risks and benefits. A patient should be encouraged to express their goals and concerns. The selection of interventions, including genetic evaluation, activity, lifestyle, and therapy choices, should be based on individual values, preferences, and associated conditions and morbidities. Judicious use of exercise, when advised, can also improve outcomes. Referral of patients to multidisciplinary HCM centers may help improve patient outcomes. Providers at HCM centers have specific training and competencies necessary to manage these patients' specialized and complex needs. Particularly with invasive SRT (ASA or SM), treatment guidelines recommend that patients have the procedure performed at comprehensive or primary HCM centers with specialized training and sufficient volumes to ensure optimal outcomes.<sup>1</sup>

### Emerging Therapies: Cardiac Myosin Inhibitors

Currently, no medical treatments that modify the pathology and disease course exist for HCM. Gene therapy with clustered regularly interspaced short palindromic repeats/clustered regularly interspaced short palindromic repeat-associated 9 (CRISPR/Cas9), exon-skipping, trans-splicing, gene replacement, or small interfering RNAs (siRNAs) may play a future role in the treatment of HCM.<sup>19</sup> Trials investigating small molecules, such as cardiac myosin inhibitors, in patients with HCM have shown promise. The phase 2 trial (REDWOOD-HCM) with CK274 is currently ongoing.<sup>20</sup> Cardiac myosin inhibitors selectively inhibit cardiac myosin ATPase and reduce myocardial contractility by decreasing the available number of actin-myosin cross-bridges. The reduction in contractility reduces the outflow gradient, which may improve symptoms.<sup>19</sup>

On January 11, 2021, the FDA granted CK274 an orphan drug designation for the treatment of symptomatic HCM.<sup>21</sup> Investigations with the cardiac myosin inhibitor mavacamten completed phase 2 clinical trial testing (MAVERICK-HCM) in patients with symptomatic nHCM and phase 3 clinical trial testing (EXPLORER-HCM) in patients with symptomatic oHCM.<sup>22,23</sup> On July 23, 2020, the FDA granted breakthrough therapy designation to mavacamten to treat symptomatic oHCM with a New Drug Application (NDA) submission expected in the first quarter of 2021.<sup>24</sup> An ongoing long-term

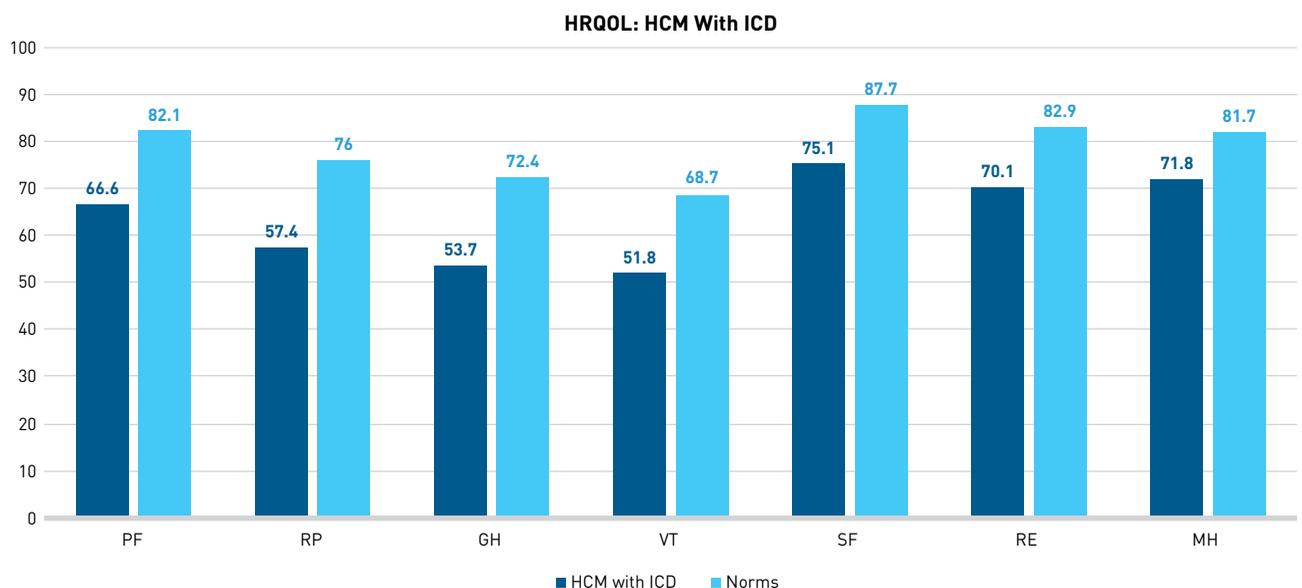
extension study, MAVA-LTE, evaluating the long-term safety of mavacamten is estimated for completion in November 2025.<sup>25</sup> These investigational therapies that target the underlying pathophysiology of HCM are not approved by the FDA yet.<sup>21,26</sup>

### Managed Care Considerations

Currently, medication therapy in patients with HCM is first-line for symptomatic control (see Figure 2<sup>1,27</sup>). The recommended management of HCM includes the use of low-cost generically available cardiac medications such as non-dilating β-blockers, non-dihydropyridine calcium channel blockers, and disopyramide. Other drugs may be used to treat HCM-associated complications, including anticoagulants for AF, antiarrhythmics for arrhythmias, and angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, angiotensin receptor-neprilysin inhibitors, mineralocorticoid receptor antagonists, and diuretics to treat HF. Patients refractory to treatment may require an ICD, SRT, or CT to treat symptoms and complications. See Figure 2 for current management of HCM.<sup>1,27</sup>

As new treatments are approved, further clinical evidence regarding their safety and efficacy is gathered before place in therapy is determined by clinical practice guidelines. Expedited FDA approval is based on data from clinical studies conducted over a shorter timeframe, sometimes raising concerns of long-term safety and

**FIGURE 1.** HRQOL: HCM With ICD Compared With General Population Norms<sup>18</sup>



GH, general health; HCM, hypertrophic cardiomyopathy; HRQOL, health-related quality of life; ICD, implantable cardiac defibrillator; MH, mental health; PF, physical functioning; RE, role emotional; RP, role physical; SF, social functioning; VT, vitality.

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efficacy.<sup>28</sup> This poses challenges for managed care professionals to allocate healthcare resource utilization responsibly and effectively. The development of informed and updated formulary strategies to treat HCM is essential to integrate pharmaceutical advances based on improved risk-benefit profiles of investigational agents.<sup>29</sup> A clinically rigorous analysis of current clinical trial data should be conducted, looking for meaningful improvement on clinically significant end points, including hospitalization and mortality, as well as hemodynamic parameters.<sup>30,31</sup> A review of available literature, including clinical treatment guidelines, pharmacoeconomic studies, and outcomes data, is essential. Other important points of consideration include analysis of FDA prescribing information and safety data, drug and total healthcare cost data, and efficacy and cost comparisons to standard of care. Comparative effectiveness data, if available, may be a valuable resource to evaluate the use of drug versus alternative treatment options. An effective formulary management process enables the managed healthcare system to discriminate between a clinically superior and a marginally effective drug, minimizing overall medical cost and promoting patient access to affordable care.<sup>29</sup>

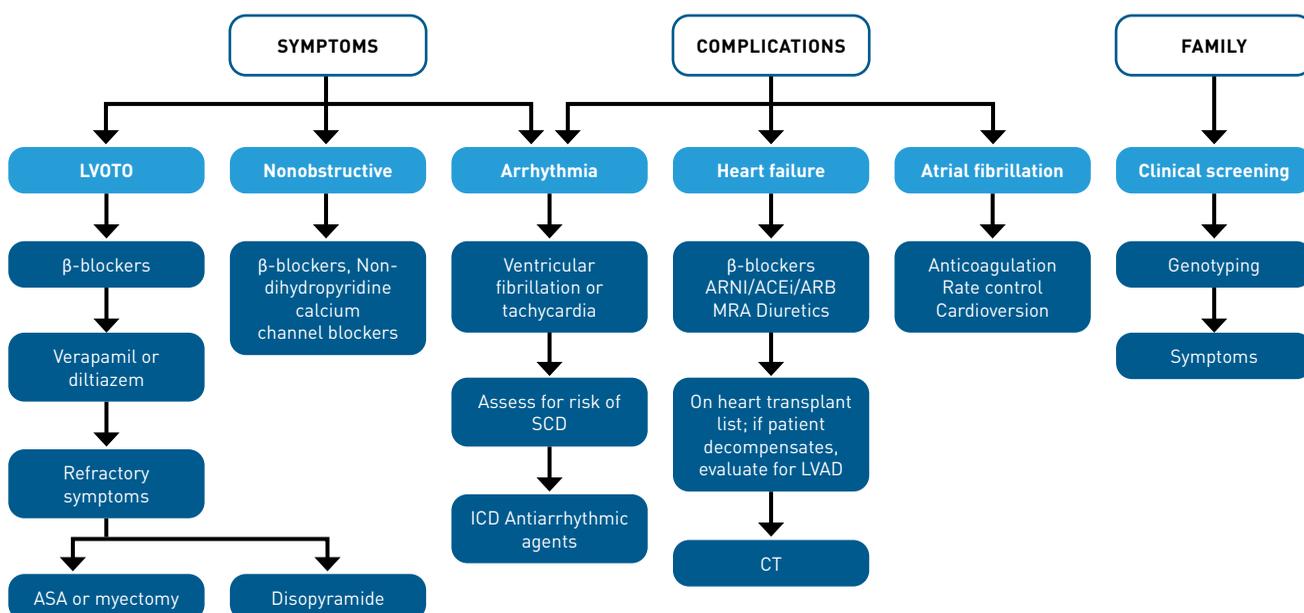
Utilization management strategies such as step therapy, quantity limits, and prior authorization (PA) may complement formulary management. Evidence-based PA criteria are crucial to ensure

patients receive the most appropriate medication for their condition while reducing unnecessary drug use and cost. This will be more evident as new agents enter the marketplace, but even among current generically available agents, there are opportunities for enhanced utilization management to influence usage to less expensive generic agents.<sup>32</sup>

### Conclusions

HCM is a disease associated with substantial economic and clinical burdens. Although improvements in earlier diagnosis, risk stratification, family screening, pharmacologic therapy, devices, and surgical management have led to better outcomes, HCM has been associated with a decreased HRQOL and psychological well-being. Thus far, management of HCM has been symptomatic and does not treat the underlying illness. Cardiac myosin inhibitors have recently shown promise in clinical trials as potential first-in-class medications to treat the underlying pathology of HCM. Managed care pharmacists should be prepared to assess their value to improve patients' length and quality of life affected by HCM and reduce medical costs for these patients. Ultimately, the results of long-term safety and efficacy studies showing reductions in hospitalizations, morbidity, and mortality compared with standard of care will determine these agents' value and place in practice. ■

**FIGURE 2.** HCM Treatment Landscape<sup>1,27</sup>



ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; ASA, alcohol septal ablation; CT, cardiac transplantation; HCM, hypertrophic cardiomyopathy; ICD, implantable cardiac defibrillator; LVAD, left ventricular assist device; LVOTO, left ventricular outflow tract obstruction; MRA, mineralocorticoid receptor antagonist; SCD, sudden cardiac death.

**Author affiliation:** Patty Taddei-Allen, PharmD, MBA, BCACP, BCGP, is the Vice President, Clinical Programs and Services, WellDyne, Lakeland, FL.

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**Address correspondence to:** ptaddei-allen@welldyne.com

**Medical writing and editorial support provided by:** Lori A. Uildriks, PharmD

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# Advancements in Treatment for Hypertrophic Cardiomyopathy: Key Considerations for Managed Care Professionals

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## Sample of Online Posttest

Choose the best answer for each of the following:

- An estimated 750,000 Americans are affected with hypertrophic cardiomyopathy (HCM), but only \_\_\_\_\_ have received a confirmatory diagnosis.**
  - 50,000
  - 100,000
  - 200,000
  - 400,000
- What are the two most frequent HCM genes responsible for 70% of patients who are variant positive?**
  - ACTC1* and *MYH7*
  - MYL2* and *TPM1*
  - MYH7* and *MYBPC3*
  - MYH7* and *MYL2*
- As sudden cardiac death (SCD) risk extends over one's lifetime with HCM, it is recommended to reassess risk every \_\_\_\_\_.**
  - 6 months to 1 year
  - 1 to 2 years
  - 3 to 4 years
  - 5 to 6 years
- Current goals of pharmacologic therapy in HCM are symptom relief and \_\_\_\_\_.**
  - Disease attenuation
  - Disease prevention
  - Alteration of the natural history
  - Improvement in quality of life
- Which of the following is considered first-line treatment for symptomatic obstructive HCM?**
  - Non-vasodilating  $\beta$ -blockers
  - Dihydropyridine calcium channel blockers
  - Thiazide diuretics
  - Vasodilators
- Mavacamten is a first-in-class, small molecule that selectively inhibits which of the following?**
  - Cardiac calcium channels
  - Cardiac muscarinic receptors
  - Cardiac myosin ATPase
  - Cardiac sodium-potassium channels
- A retrospective cohort study by Jan et al assessing the cost of managing patients admitted to the hospital with an obstructive hypertrophic cardiomyopathy (oHCM) diagnosis found that approximately \_\_\_\_ of the patients in the study required further institutionalized care.**
  - One-half
  - Two-thirds
  - One-quarter
  - One-fifth

8. HM is a 20-year-old man who recently underwent genetic testing for HCM. His brother died of SCD at 17 years old while playing football. Autopsy determined that his brother's cause of death was due to HCM. Genetic testing for HM reveals a sarcomeric mutation of gene variant *MYH7*. Based on the study results by Ho, HM's risk for adverse outcomes is expected to be approximately \_\_\_\_ times.
- A. Three
  - B. Four
  - C. Five
  - D. Ten
9. PM is a 65-year-old patient with a diagnosis of oHCM. Conservative therapy with  $\beta$ -blockers and verapamil has failed. The patient goes to her cardiologist for a visit. Her cardiologist is not affiliated with an HCM center. How should her cardiologist approach the next treatment steps in this patient to improve outcomes consistent with HCM guideline recommendations?
- A. The cardiologist should tell PM she will die without surgical intervention.
  - B. The cardiologist should talk about the available treatment options, discussing all the risks and benefits. The physician recommends postponing further treatment.
  - C. The cardiologist should refer PM to a high-volume HCM center to perform an alcohol septal ablation (ASA) as soon as possible.
  - D. The cardiologist should talk about the available treatment options, discussing all the risks and benefits. Both PM and physician agree a septal myectomy (SM) would be best to manage her disease. The cardiologist should refer PM to a high-volume HCM center for consultation.
10. In a study by Lemor et al, patients older than 65 years undergoing SM had approximately \_\_\_\_ times the risk for in-hospital mortality versus those undergoing ASA.
- A. 2
  - B. 3
  - C. 4
  - D. 6



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