Learning Objectives
At the end of this Clinical Review, the learner will be better able to:

1. Recognize and evaluate the pathophysiology of hypertrophic cardiomyopathy (HCM).
2. Communicate the need to discuss genetic testing of patients with identified and suspected HCM.
3. Identify patients who require HCM treatment and discuss the relevant treatment options.
4. Identify patients and family members who should undergo continuing cardiac and/or clinical screening and testing for HCM.
5. Identify family members who do not need continuing clinical surveillance.

Target Audience
Target audience includes healthcare professionals involved in the care of patients with hypertrophic cardiomyopathy (HCM).

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Dr. de Feria received his MD from Vanderbilt University. He completed his internal medicine training at Brigham and Women’s Hospital prior to joining the University of Pennsylvania for his cardiovascular medicine training. He has been an active member of the American Heart Association, having been a member of the 2022 AHA Roundtable on HCM. He is also actively involved with the Hypertrophic Cardiomyopathy Association (HCMA), a patient-led organization dedicated to improving the lives of those with HCM.

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Disclosures

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Hypertrophic cardiomyopathy (HCM) is the most common and most commonly misunderstood genetic cardiac disease.\textsuperscript{1} It was once thought to occur in about 1:500 of the general population. Based on echocardiographic analyses in unrelated young adults, genetic testing, detailed familial screening and advanced imaging, a prevalence that could be as high as 1:200.\textsuperscript{2} At the same time, most people with HCM are unaware of their disease.

Data from the late 20th century showed annual HCM mortality as high as 6%, leaving too many patients and clinicians believing that HCM is an ominous diagnosis associated with an unfavorable prognosis, unrelenting progression and no effective treatment strategies.\textsuperscript{4} The reality is that current treatment approaches have reduced HCM-related mortality to 0.5% per year, comparable to the general population.\textsuperscript{5} Despite the improvements in mortality, recent studies have shown that ≈8% of patients with HCM will develop left ventricular systolic dysfunction, also known as “end stage” HCM.

HCM is often a monogenic, autosomal dominant disorder associated with at least 26 genes, most encoding thick and thin filament proteins of the cardiac sarcomere.\textsuperscript{5,6} These mutations occur without regard to race, ethnicity, sex or global geography.\textsuperscript{7} First-degree relatives of individuals with HCM who carry pathogenic variants are at 50% risk of inheriting the pathogenic variant, being genotype-positive. Many individuals who are genotype-positive may never develop or recognize cardiovascular symptoms, experience any adverse HCM-related events or be identified with other clinical markers such as abnormal electrocardiogram or family history.\textsuperscript{2,8}

Up to 60% of patients with HCM have an identifiable pathogenic or likely pathogenic variant. The remainder have no currently identified genetic etiology associated with their disease, including individuals with no other affected family members. More than 1,500 variants of the most common causal genes (MYH7, MYBPC3, TNNI3, TNNT2, TPM1, MYL2, MYL3 and ACTC1) have been identified, most unique to individual families. The age of onset of HCM, if symptoms ever appear, is highly variable and genotypes do not accurately predict individual outcomes.\textsuperscript{1}

HCM is a heterogeneous disorder characterized by left ventricular hypertrophy (LVH) in the absence of other cardiac, systemic or metabolic disease capable of producing similar LVH. Systemic and metabolic confounders (also known as phenocopies) include RASopathies, mitochondrial myopathies and glycogen/lysosomal storage diseases in children as well as Fabry, amyloid, sarcoid, hemochromatosis and Danon cardiomyopathy in adults. Conditions that can produce secondary LVH such as cardiac remodeling secondary to intensive athletic training (athlete’s heart) as well as morphologic changes related to chronic systemic hypertension (hypertensive cardiomyopathy), hemodynamic obstructions caused by left-sided obstructive lesions (valvular or subvalvular stenosis), obstruction after antero-apical infarction and stress cardiomyopathy can also confound diagnosis.\textsuperscript{1}

Potential outcomes from HCM are quite varied, ranging from sudden cardiac death, myocardial infarction, AFib, other arrhythmias and heart failure to asymptomatic survival with normal life expectancy.\textsuperscript{2} Most patients with HCM develop left ventricular outflow tract obstruction (LVOTO) over time, but about one-third remain unobstructive.\textsuperscript{1} Both obstructive and unobstructive patients can exhibit a range of symptoms.

Clinical evaluation for HCM is often triggered...
by the occurrence of symptoms, a cardiac event, detection of a heart murmur, an abnormal 12-lead ECG seen on routine exam or cardiac imaging during family screening studies. In adults, imaging with 2D echocardiography or cardiovascular magnetic resonance (CMR) showing a maximal end-diastolic wall thickness of >15mm anywhere in the left ventricle without another cause for hypertrophy establishes a clinical diagnosis of HCM. More limited hypertrophy, 13-14mm, may be diagnosed in individuals who have a known family history of HCM or are identified as carrying a pathogenic or likely pathogenic variant associated with HCM.

Younger age at diagnosis and the presence of a sarcomere mutation are strong predictors of lifetime adverse events, although most events occur later in life. Between 30% and 40% of patients with HCM can expect to experience adverse events during their lifetimes, including sudden death, progressive limiting cardiac symptoms, heart failure, AFib, ventricular arrhythmia and stroke. The pathophysiology of HCM includes LVOTO, mitral regurgitation, diastolic dysfunction, myocardial ischemia, arrhythmias and autonomic dysfunction. Clinical outcomes may be dominated by a single component or the interplay of multiple components. Clinical evaluation should include a comprehensive cardiac history, a three-generation family history to identify relatives with HCM or unexpected/sudden death and a comprehensive physical exam, including physical exertion maneuvers such as Valsalva, squat-to-stand, passive leg raising or walking. Any suggestive findings should trigger ECG and cardiac imaging.

Diagnosis can be more difficult in children due to adjustments for body size and growth. While a body surface area adjusted z-score of ≥2 standard deviations above the mean is the traditional diagnostic HCM cut-off for children, more recent data suggest z ≥2.5 standard deviations is more useful in children who are asymptomatic and have no family history of HCM. For children with a positive genetic test or definitive family history, z ≥2 may be diagnostic.

CMR provides high spatial resolution and assessment of myocardial fibrosis with the use of late gadolinium enhancement (LGE) contrast. Because CMR shows sharp contrast between the blood pool and myocardium, it can provide more accurate measurements of LV wall thickness and identify areas of LVH not well-visualized by echocardiography, including the anterolateral wall, posterior septum and apex. Discussion of genetic testing is standard in patients with identified HCM. First-line genetic testing consists of targeted gene panels that include known disease-causing HCM variants. Exome sequencing and whole genome sequencing may be considered as second tier testing if no causal variant is identified on initial targeted testing. Current technology can identify a pathogenic variant in about 30% of sporadic cases and 60% of familial cases by searching for the eight most common genes, MYH7, MYBPC3, TNNI3, TNNT2, TPM1, MYL2, MYL3 and ACTC1.

All first-degree relatives of those diagnosed with HCM should be advised to undergo clinical screening for HCM. If a pathogenic or likely pathogenic variant is identified in the proband, this is a clinically actionable finding which can be utilized by first degree relatives for more predictive risk stratification. Family members who do not carry the familial disease-causing variant do not need continued clinical surveillance. Family members who carry the pathogenic or likely pathogenic variant should undergo clinical screening with ECG and echocardiography at the time they receive their genotype-positive status followed by regular interval screening. Children and adolescents should be screened every 1-2 years, and adults every 3-5 years. This would also be true when there is no pathogenic variant identified in the family member with HCM or if genetic information is not available.
Identifying a variant of uncertain significance (VUS) is not clinically actionable but may be useful for research purposes. Classification of a VUS can change over time, so re-reviewing these variants periodically may prove meaningful over time.

Individuals who carry a pathogenic or likely pathogenic HCM-causing gene variant but are both asymptomatic and show no signs of LVH on cardiac imaging are genotype-positive, phenotype-negative. They may also be described as having preclinical HCM. All need ongoing cardiac surveillance for progression to clinical HCM. Up to 15% of patients develop clinical HCM before the age of 18, and a third of patients who develop clinical HCM need medical, surgical or device therapy before age 18.

HCM can lead to sudden cardiac death (SCD) in younger individuals, but is rare in genotype-positive, phenotype-negative patients. Established clinical risk factors for SCD include family history of SCD from HCM, massive LVH (≥ 3cm), unexplained syncope, HCM with LV systolic dysfunction, LV apical aneurysm, extensive LGE on CMR imaging and non-sustained ventricular tachycardia (NSVT). Patients at high risk for SCD may be good candidates for ICD placement for primary prevention. Because the risk of SCD extends over many decades of life, patients need periodic reassessment and discussion of SCD risk.

Conventional pharmacologic therapy does not appear to alter the natural history of HCM but may provide symptom relief for patients with LVOTO. Maximum tolerable doses of nonvasodilating beta blockers are first-line therapy, with calcium channel blockers verapamil or diltiazem reasonable alternatives. Disopyramide can be also be utilized given its anti-inotropic effects, although tolerance is often limited by significant anti-cholinergic side effects such as dry mouth and eyes, constipation and urinary retention. These side effects can often be reduced with the use of pyridostigmine. Disopyramide can prolong QT interval and be pro-arrhythmic, so is often initiated inpatient. It is vital to eliminate medications that may provoke outflow tract obstruction, including pure vasodilators (dihydropyridine class calcium channel blockers, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers) and high dose diuretics.

Patients who remain symptomatic on standard pharmacologic therapy may consider mavacamten, a cardiac myosin inhibitor approved by the Food and Drug Administration in April 2022 to improve functional capacity and symptoms in adults with symptomatic NYHA class II–III obstructive HCM. Compared to placebo in the pivotal EXPLORER-HCM trial, patients taking mavacamten showed improved peak oxygen consumption and/or improvement in NYHA status. Individuals taking mavacamten also showed greater improvement in quality-of-life as measured by Kansas City Cardiomyopathy Questionnaire versus placebo.

Mavacamten was generally well-tolerated in clinical trials, although 88% of patients in EXPLORER-HCM reported treatment-emergent adverse events, primarily dizziness and syncope. The most frequent serious adverse events included AFib, syncope and stress cardiomyopathy (all 2%).

The FDA approval of mavacamten included a black box warning for risk of heart failure due to systolic dysfunction, a risk of reduced ejection fraction, and contraindications for concomitant use of some CPY450 inhibitors and inducers due to an increased risk of heart failure. The drug is available only through a risk evaluation and mitigation strategy, CAMZYOS™ REMS. Prescribers, patients and pharmacies must all enroll in the CAMZYOS REMS program.

Results of the VALOR-HCM trial results suggest mavacamten may offer a viable alternative to septal reduction therapy (SRT) for carefully selected patients with more severe symptoms.
Among patients with obstructive HCM with NYHA class III-IV symptoms (or class II with syncope) who met guideline criteria for SRT, just 17.9% met guideline criteria for SRT after 16 weeks of mavacamten treatment compared to 76.8% of patients on placebo. Long-term freedom from SRT has yet to be determined.\(^1\)

SRT is considered for patients with severe outflow tract obstruction who remain symptomatic despite maximal tolerable medical therapy. Transaortic extended septal myectomy can treat a broad range of symptomatic patients with obstructive HCM. Experienced operators at high volume comprehensive HCM centers demonstrate clinical success >90-95% with mortality <1%. Long-term survival after surgical myectomy is similar to an age-matched general population.\(^1\) Myectomy via an apical approach can be utilized in combination with transaortic myectomy to treat septal hypertrophy not confined to the basilar septum and/or for patients with mid-cavitary obstruction.\(^13\) Apical myectomy can also be useful for patients with apical predominant hypertrophy wherein the primary pathology is reduced LV cavity size and therefore low stroke volume, even in the absence of outflow obstruction.\(^13\)

The mitral valve and subvalvar apparatus can also contribute significantly to the pathophysiology of LVOTO in HCM and are potential surgical targets. Many patient with LVOTO have a component of Systolic Anterior Motion (or “SAM”) of the mitral valve that contributes to the blockage of blood trying to leave the heart. In almost every patient with HCM and LVOTO, the posteromedial papillary muscle is apically displaced and abnormally bound to the ventricular septum and posterior wall of the ventricle. This can easily be sharply mobilized during surgery and may place the anterior leaflet of the mitral valve in a more favorable position. Many patients will also have accessory chordae from the mitral valve or submitral apparatus that insert into the ventricular septum, thereby “tethering” the anterior leaflet in an unfavorable position and potentiating SAM. These can also be easily excised during surgery. Some patients have an abnormally long anterior mitral valve leaflet and be predisposed to SAM even following surgery. Edge-to-edge mitral valve repair, also known as an “Alfieri Stitch” can be performed for such patients to prevent persistent SAM.\(^14\)

Alcohol septal ablation offers a noninvasive alternative for patients who are not surgical candidates. Appropriate coronary anatomy is necessary, and alcohol septal ablation should be completed by an experienced interventional cardiologist. This procedure may be less effective for high resting gradients or septal thickness ≥30 mm and may also carry a higher risk of complete heart block, necessitating implantation of a pacemaker.\(^1\)

There is potential for increased risk of thromboembolism in the setting of HCM. If AFib is detected, anticoagulation is recommended regardless of CHA2DS2-VASc score. Direct acting oral anticoagulants (DOACs) are first line, with warfarin as a second-line option.\(^1\)

HCM with associated heart failure can be challenging to manage. Diastolic dysfunction often results from chamber stiffness, altered ventricular load, nonuniform contraction and relaxation, and smaller ventricular size. Diuretics may be needed if there are signs/symptoms of congestion, but this must be done cautiously, especially if there is known dynamic obstruction.\(^1\) Some with HCM will develop “burnout HCM” when LVEF is <50%. Aggressive management with traditional guideline-directed medical therapy for heart failure with reduced ejection fraction should then be initiated. An LVEF <50% is also a risk factor for SCD.\(^1\) Patients with an LVEF <50% may have a higher symptom burden with an only mildly reduced LVEF and should be managed as advanced disease. Consider sending to a transplant center for consultation.
The success of ICD placement and SRT have shifted long-term management efforts to HCM patients with AFib, ventricular arrhythmias and heart failure. The presence of HCM has minimal impact on the clinical management of AFib, ventricular arrhythmias or heart failure. For most patients with HCM, mild to moderate intensity physical activity is beneficial and leads to improved cardiorespiratory fitness, physical functioning, quality of life and overall health. Athletes with HCM may benefit from a comprehensive evaluation and discussion of the potential risks of sports participation. ICD placement for the sole purpose of participation in competitive sports should not be performed.

References:
CLINICAL REVIEW | Hypertrophic Cardiomyopathy

CASE STUDY 1 MIKE

Existing HCM with AFib, Rheumatoid Arthritis and Worsening Shortness of Breath

Mike is a 54-year-old man who came in for evaluation due to increased breathlessness since his last AFib ablation. He was diagnosed with obstructive HCM around age 35 after he had a murmur found on exam. He was intermittently followed by cardiology, but there were never significant concerns regarding his HCM as he had overall been stable. His echocardiogram at diagnosis showed an interventricular septal wall thickness of 2 cm, a left ventricular posterior wall thickness of 1.0 cm, and a peak LVOT gradient of 40 mmHg with Valsalva. He was managed with 50 mg of metoprolol and 120 mg of verapamil for many years.

At age 50, he presented to the emergency room with chest pain and was found to be in rapid AFib. He was started on amiodarone and soon underwent ablation. He remained in sinus rhythm until about a year ago, at which time he started having recurrent bouts of AFib.

His echocardiogram at an outside institution prior to cardioversion showed an LVEF of 30% in the setting of rapid AFib. He has now undergone a second AFib ablation and is maintained on sotalol, metoprolol, and apixaban. He is treated for RA with methotrexate and has mildly abnormal renal function with a creatinine of 1.4.

He came in for outpatient follow-up today, as it has been three months since his ablation. His HR is 65, BP 102/76, RR 12, oxygen saturation 98% on room air. He describes being less active than he was a year ago, now getting short of breath when climbing a flight of stairs. An echocardiogram was completed today in sinus rhythm showing an EF of 45%, left ventricular end diastolic dimension of 5.6 cm, IVS 1.3 cm, LVPW 0.9 cm, and LA volume index of 48 ml/m2. He also underwent cardiac MRI, which showed an EF of 45% and extensive delayed gadolinium enhancement comprising 30% of the left ventricular myocardium. He is wondering if his progressive symptoms are due to bradycardia or worsening rheumatoid arthritis. He has been told his cardiac hypertrophy has improved and his rhythm is now controlled.
Questions:

1. What additional testing will be most helpful to determine symptoms?
   a. Repeat echocardiogram on less beta blocker
   b. Extended holter monitoring
   c. Combined cardiopulmonary exercise testing with stress echocardiogram
   d. Referral to pulmonary

2. Should an ICD be considered?
   a. No, the EF is >35%
   b. No, there is no history of NSVT or syncope
   c. Yes, the EF is <50%
   d. Yes, he has a history of AFib

3. What medical therapy should be initiated?
   a. Valsartan
   b. Continue verapamil
   c. Digoxin
   d. Mavacamten

4. What is not a risk factor for development of systolic dysfunction in HCM?
   a. Multiple pathogenic sarcomeric variants
   b. Massive left ventricular hypertrophy
   c. EF 50-59%
   d. Advanced age at diagnosis
Richard is a 48-year-old man with well-controlled hypertension. For the past few months, he has noticed a left-sided, non-radiating chest discomfort with exertion that is relieved by rest. The chest discomfort is associated with exertional dyspnea and sometimes dizziness, but no diaphoresis or nausea. Symptoms can occur with activities such as carrying objects, walking up inclines or walking quickly. He may occasionally feel a “heart flutter” without associated symptoms. He denies presyncope, syncope, edema, orthopnea and paroxysmal nocturnal dyspnea. His home blood pressures are typically 120s/80s mmHg. Because a murmur was auscultated, an electrocardiogram (ECG), a resting transthoracic echocardiogram and a coronary CTA were ordered.

**Past Medical History:** Hypertension diagnosed four years ago.
**Medications:** Amlodipine 5 mg daily.
**Allergies:** No known drug allergies.
**Social History:** He works as an automobile mechanic. He denies a history of smoking, alcohol abuse and illicit substance use.

**Family History:** He has a 15-year-old son who plays high school basketball and is well. He has two full biological siblings. His sister Leah is 52 years old and has been seen for an “irregular heart beat,” but he does not know details. She has had tests for her heart, but he thinks they were normal. She has two children who are well. A younger brother Todd is 45 years old and has no known heart problems or symptoms. This brother has three children who, to his knowledge, are healthy. Richard’s mother died of a “heart attack” at 52 years of age. She did not have risk factors for coronary artery disease, and he does not think an autopsy was done. His maternal grandparents lived into their 80s. He has one maternal aunt who is in her 70s with congestive heart failure (CHF). His maternal grandmother had a brother who died in his 30s, but he is not sure of the details. His father is 77 years old. He has a “heart stent” and is under the care of a cardiologist. His paternal grandfather was in a car accident in his 70s. His paternal grandmother had a stroke in her 70s and died a few years later. There is no significant paternal family history of sudden cardiac death or premature heart disease.

**Exam:** BMI 32, BP 115/78 mmHg, P 95 bpm, R 18.
**General:** Appears normal and no apparent distress.
**Neck:** JVP ~6-8 cm above left atrium.
**Heart:** Regular heart rate and rhythm, II/VI systolic crescendo decrescendo murmur that increases with Valsalva.
**Resp:** Lungs clear to auscultation without adventitious breath sounds bilaterally.
**Extremities:** No lower extremity edema, palpable pulses bilaterally.

**Labs:** eGFR > 90 mL/min, creatinine 0.8, K 4.0, high sensitivity troponin T 15, NT-proBNP 200.
**ECG:** Sinus rhythm at 80 bpm with left ventricular hypertrophy (LVH), abnormal Q waves anterior leads and ST elevation anterior leads.

**Family History Suggestive of HCM**

Richard’s family history is suggestive of hypertrophic cardiomyopathy (HCM). His maternal aunt has CHF, and his maternal grandmother had an “irregular heart beat.” His maternal grandfather died in his 30s, and he does not know the details. His father has a “heart stent” and is under the care of a cardiologist. His maternal grandmother had a brother who died in his 30s, but he is not sure of the details. His father is 77 years old. He has a “heart stent” and is under the care of a cardiologist. His paternal grandfather was in a car accident in his 70s. His paternal grandmother had a stroke in her 70s and died a few years later. There is no significant paternal family history of sudden cardiac death or premature heart disease.

**CASE STUDY **

**RICHARD**

2

Continued
**ECHO:** Asymmetric septal hypertrophy up to 1.9 cm and posterior wall 0.9 cm, left ventricular ejection fraction (LVEF) 65%, enlarged LA, LVOT gradient 20 mmHg at rest and 49 mmHg with Valsalva strain, systolic anterior motion (SAM) of the mitral valve with mild regurgitation, trace tricuspid regurgitation and inferior vena cava (IVC) diameter <2.1 cm that collapses >50%.

**Coronary CTA:** Calcium score 0. No coronary atherosclerosis. You diagnose obstructive HCM.
Questions:

1. What would be most reasonable next step in medical management?
   a. Add metoprolol tartrate and continue amlodipine
   b. Change amlodipine to verapamil
   c. Initiate disopyramide as an inpatient
   d. Start a myosin inhibitor

2. What testing will help with risk stratification for sudden cardiac death?
   a. Holter monitor
   b. Cardiac MRI
   c. Exercise stress echocardiogram
   d. Pharmacological nuclear MPS
   e. A and B
   f. A, B and C

3. What is most concerning regarding his risk for sudden cardiac death?
   a. Family history
   b. Septum 19 cm
   c. Palpitations
   d. Exertional symptoms

4. Whom should the patient be made aware that they may see after referral to an HCM Center of Excellence?
   a. Cardiologist
   b. Electrophysiologist
   c. Genetic counselor
   d. All of the above
Because Richard went on to have genetic testing and was found to have a pathogenic variant in MYBPC3, his sister Leah has come to you for evaluation. Leah is a 52-year-old female with a history of paroxysmal AFib, obstructive sleep apnea (OSA) on continuous positive airway pressure (CPAP) therapy, hypertension, obesity and hyperlipidemia. An echocardiogram five years ago when she was diagnosed with AFib showed normal LVEF, concentric LVH and left atrial (LA) enlargement. She was told the LVH was from high blood pressure and being overweight. She also had a pharmacological nuclear MPS at the time, which showed no evidence of ischemia secondary to epicardial coronary artery disease.

Leah now reports worsening dyspnea after walking about a block but denies chest pain. Although she has noticed increased lower extremity edema at the end of the day for several years, it no longer resolves by the next morning. She sleeps on an incline for back comfort and does wear her CPAP mask. She has not felt her palpitations like those she experienced when she had AFib for several months. She denies dizziness and syncope. She has noticed weight gain of about 15 pounds in the past couple of months.

**Past Medical History:** Paroxysmal AFib never requiring electrical cardioversion, OSA on a CPAP, hypertension, obesity, hyperlipidemia.

**Medications:** Aspirin 81 mg daily, metoprolol tartrate 50 mg daily, diltiazem CR 180 mg daily, losartan 100 mg daily, atorvastatin 40 mg daily. 
**Allergies:** Cough on ACE inhibitor. 

**Social History:** She is a homemaker and is on her husband’s commercial health insurance. She denies a history of smoking, alcohol abuse and illicit substance use. 

**Family History:** She has a daughter who is 27 years old and pregnant. She is well. Her other daughter is 24 years old. This daughter passed out a few times in elementary school but has not for several years. She takes medication for her blood pressure. See Richard’s case study for the remainder of the family history.

**Exam:** BMI 48, BP 130/78 mmHg, P 70 bpm, R 18. 

**General:** Appears normal and no apparent distress. 

**Neck:** JVP ~12-15 cm above left atrium. 

**Heart:** Regular heart rate and rhythm, no murmur at rest or with Valsalva maneuver. 

**Resp:** Bilateral crackles in lower lobes. 

**Extremities:** Bilateral 1+ lower extremity edema, palpable pulses bilaterally. 

**Labs:** eGFR > 90 mL/min, creatinine 0.6, K 4.5, high sensitivity troponin T 16, NT-proBNP 1,000. 

**ECG:** Sinus rhythm at 63 bpm with LVH and T-wave inversions in anterolateral leads.
**CASE STUDY**

**ECHO:** Poor imaging quality. Contrast imaging not performed for unclear reasons. LVEF 55%, concentric LVH up to 1.4 cm, no resting LVOT obstruction. Valsalva maneuver images not recorded. No significant valvular disease. IVC not well visualized.

Stress echocardiogram for obstruction: Achieved 4.3 METs. Exercise was terminated because of dyspnea. Appropriate hemodynamic response, no arrhythmia, no significant LVOT obstruction at rest, Valsalva or exertion. Mid-LV cavity gradients 10 mmHg rest, 18 mmHg Valsalva and 22 mmHg post-exercise.

**CMR:** Hyperdynamic systolic function, mid/apical LV hypertrophy up to 2.1 cm at the apex, apical cap is thinned/aneurysmal and dyskinetic, normal RV and hyperdynamic function, mild MR and abnormal with patchy delay enhancement involving the mid anterior wall, apical lateral and inferior wall.

You diagnose apical variant HCM.
**Questions:**

1. **Which statement regarding anticoagulation is most appropriate for Leah?**
   
   a. Continue aspirin 81 mg daily because her CHA2DS2-VASc score is only 1 from hypertension
   
   b. Start a NOAC for LV aneurysm and AFib regardless of CHA2DS2-VASc
   
   c. Warfarin is indicated for the apical aneurysm but not for AFib because of her CHA2DS2-VASc score
   
   d. Continue aspirin and start a NOAC

2. **Whom should Leah see soon?**
   
   a. Interventional cardiologist for ischemia evaluation
   
   b. Cardiothoracic surgeon for apical aneurysm resection
   
   c. Electrophysiologist for ICD given family history, fibrosis, and apical aneurysm
   
   d. Electrophysiologist for a pacemaker so that beta-blockers and calcium channel blockers can be up-titrated

3. **What additional medication interventions may improve Leah’s symptoms?**
   
   a. Furosemide 20 mg daily
   
   b. Hydrochlorothiazide 25 mg daily
   
   c. Change metoprolol to carvedilol
   
   d. Change diltiazem to verapamil

4. **What statement about HFrEF management in HCM is true?**
   
   a. Diuretics are contraindicated in HCM and should never be used
   
   b. Thiazide diuretics are preferred over loop diuretics or MRA antagonists
   
   c. Diuretics are needed only when LVEF < 50%
   
   d. Diuretics could provoke LVOTO or mid-cavitary obstructions

5. **What is the most likely result of genetic testing for Leah and why?**
   
   a. Positive for the familial pathogenic variant because she also HCM
   
   b. Negative for the familial pathogenic variant but positive for another variant because she does not have the same pattern of hypertrophy as her brother
   
   c. Positive for the familial pathogenic variant and positive for another variant because she has more severe HCM
   
   d. Negative for any pathogenic variant because apical HCM is not typically associated with identifiable genetic variants
Collette is a 57-year-old woman with HCM and LVOTO that was initially diagnosed 10 years prior when she had a screening echocardiogram as a participant in a clinical trial. Her symptoms of exertional dyspnea have been worsening over the past 12 months and are now NYHA class II on a good day and class III on a bad day. A recent stress echo revealed a peak LVOT gradient in excess of 100 mmHg and a hypotensive response to exercise. She denies angina. Her goal is to be able to hike 5 miles.

Past Medical History: Polycystic Kidney Disease (baseline Cr ~1.5), hypertension, hyperlipidemia, hyperparathyroidism, Schatzki’s Ring.
Medications: Metoprolol 50mg TID; Valsartan 40 mg QDay; Tolvaptan: 60mg QAM, 30mg QPM; Evolocumab:140 mg q 2 weeks.
Surgical History: Parathyroidectomy.
Allergies: Atorvastatin -> myalgia.
Social History: She is a nurse by training and currently works in the insurance industry. Never smoked. Social, non-daily, alcohol consumption. No drugs of abuse or recreation.
Family History: No history of HCM. Ischemic heart disease in several paternal uncles.

Exam: BP 94/56 mmHg, P 54 bpm, R 16, BMI 29.7.
General: Appears normal and no apparent distress.
Neck: No JVD on exam.
Heart: Regular heart rate and rhythm, III/VI systolic crescendo decrescendo murmur that increases following Valsalva.
Resp: Lungs clear to auscultation without adventitious breath sounds bilaterally.
Extremities: No lower extremity edema, palpable pulses bilaterally.
Labs: Na 141, K 4.5, Cl 104, CO2 27, BUN 28, Cr 1.51, Glucose 90; Wbc, 6.2; Hgb 11.4; Hct 35; Plt 211.
LFT’s: all wnl.

Continued
CASE STUDY

EKG:

TTE:

Diastole

Systole

LVOT doppler
Questions:

1. What would be the most traditional next step in medical management?
   a. Add mavacamten
   b. Add disopyramide
   c. Stop valsartan
   d. Add diuretic

2. What pre-operative testing is most important for this patient?
   a. Holter monitor
   b. Pulmonary Function testing
   c. Exercise stress echocardiogram
   d. Coronary angiogram
   e. A and D
   f. B and D
   g. C and D

3. What factor best predicts superiority of surgical vs catheter based septal reduction therapy in this patient?
   a. Renal disease
   b. Septal thickness
   c. Systolic anterior motion (SAM) of the mitral valve
   d. History of parathyroid disease

4. Myectomy is performed. No accessory chordae from the mitral valve to the septum are appreciated and the post-CPB TEE shows residual SAM and provoked peak gradient of 45 mmHg. The maximal remaining septal thickness is 11mm. The patient is DDD paced with temporary epicardial wires for complete heart block in a 3:1 pattern. What is the best next step?
   a. Finish the operation and plan medical management for residual LVOTO
   b. Edge-to-edge repair of the mitral valve (Alfieri stitch)
   c. Place permanent epicardial pacemaker system
   d. B and C

5. The patient arrives in the ICU and is no longer pacer dependent. Vital signs are normal, the hemodynamics are appropriate and cardiac output is excellent by clinical assessment. The intensivist calls because the routine post-operative EKG shows a new left bundle branch block. What is the best next step?
   a. Do nothing
   b. Repeat the EKG while using atrial pacing wires to increase rate to 100 bpm
   c. Trend troponin levels
   d. Arrange for cardiac catheterization to evaluate for coronary ischemia
Case 1

Question 1

C. Order a CPET with stress echocardiogram. In HCM patients, reduced LV function (<50%) is associated with significant increase in morbidity and mortality. CPET provides an assessment of cardiovascular, pulmonary, and muscle performance. The results of peak oxygen consumption and anaerobic threshold can help predict progression to advanced heart failure and need for transplantation. Decreasing beta blocker is unlikely to provide improvement in symptoms or left ventricular function. Extended holter would provide less benefit as the patient is symptomatic despite sinus rhythm. The patient has no clear history to suggest pulmonary referral is relevant, and CPET provides assessment on pulmonary limitation.

Section 8.5: 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy. J Am Coll Cardiol. 2020 Dec, 76 (25) e159–e240

Case 1

Question 2

C. Yes, an ICD should be considered. Class IIA recommendations for ICD implantation in HCM include: massive LV hypertrophy ≥30 mm, history of suspected cardiac syncope, LV apical aneurysm, systolic dysfunction with ejection fraction (EF) <50%, or family history of sudden cardiac death due to HCM.


Case 1

Question 3

A. Valsartan should be initiated. HCM patients with EF<50% should be treated with standard goal directed medical therapy for heart failure. Verapamil should be discontinued. There is no clear role for initiation of digoxin. Mavacamten is a myosin inhibitor and would exacerbate systolic dysfunction in this patient.

Section 8.5: Management of Patients with HCM and Advanced HF. 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy. J Am Coll Cardiol. 2020 Dec, 76 (25) e159–e240

Case 1

Question 4

A. In a large, multicenter international registry of HCM patients, 8% of HCM patients were found to progress to “end stage” HCM. In this cohort, risk factors for development of left ventricular systolic dysfunction included: multiple pathogenic/likely pathogenic sarcomeric variants, AFib, and left ventricular ejection fraction <35%. This cohort also found that patients who developed systolic dysfunction tended to be diagnosed at a younger age.

Hypertrophic Cardiomyopathy With Left Ventricular Systolic Dysfunction: Insights From the SHaRe Registry. https://doi.org/10.1161/CIRCULATIONAHA.119.044366 Circulation. 2020;141:1371–1383

Existing HCM With AFib, Rheumatoid Arthritis, and Worsening Shortness of Breath
Family History Suggestive of HCM

Case 2

Question 1

B. Whenever possible, it is advisable to avoid medications that may exacerbate LVOT obstruction such as diuretics or vasodilators, including dihydropyridine calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers. Because verapamil and diltiazem are helpful in reducing LVOT obstruction and managing concomitant hypertension, it is reasonable to replace amlodipine with verapamil. Beta-blockers can be added later as well if the patient’s heart rate allows.

Section 8.1: 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy. J Am Coll Cardiol. 2020 Dec, 76 (25) e159–e240

Case 2

Question 2

F. A Holter monitor will provide premature ventricular complex (PVC) burden and screen for nonsustained ventricular tachycardia (NSVT). A cardiac MRI offers a more accurate assessment of maximum left ventricular hypertrophy, especially at the apex, left ventricular ejection fraction, left atrial size, and left ventricular aneurysm. It also quantifies myocardial fibrosis, which cannot be done by echocardiography. An exercise stress echocardiogram will provide objective information on exertional symptoms and functional capacity, which may guide therapy. In addition, it will provide information on hemodynamic response to exercise and exercise-induced LVOT obstruction or arrhythmias. Each of these are risk factors for sudden cardiac death in HCM. Unless there is a strong suspicion for concomitant coronary artery disease, assessments for ischemia such as a pharmacological nuclear MPS are not indicated. Furthermore, myocardial perfusion studies are susceptible to artifacts because of asymmetric hypertrophy.

Sections 6.5, 6.6 and 7: 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy. J Am Coll Cardiol. 2020 Dec, 76 (25) e159–e240

Case 2

Question 3

A. Sudden death possibly attributable to HCM in a first-degree relative or other relatives less than 50 years old is a major risk factor for sudden cardiac death. Other major risk factors are left ventricular hypertrophy of at least 3.0 cm, unexplained syncope, apical aneurysm, or LVEF < 50%.

Section 7: 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy. J Am Coll Cardiol. 2020 Dec, 76 (25) e159–e240

Case 2

Question 4

D. HCM centers are multidisciplinary and can include professionals with respective expertise in each of these areas.

Section 5: 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy. J Am Coll Cardiol. 2020 Dec, 76 (25) e159–e240
ANSWERS 3

Type 2 DM and Worsening Nephropathy

Case 3

Question 1
B. The stroke risk for patients with HCM and AFib is independent of CHA2DS2-VASc score. Direct oral anticoagulants are at least as effective as warfarin with other advantages such as patient satisfaction. Anticoagulation should also be considered for patients with an apical aneurysm. Aspirin is not currently indicated.

Section 8.3 and 8.4: 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy. J Am Coll Cardiol. 2020 Dec, 76 (25) e159–e240

Case 3

Question 2
C. An ICD is a class IIa indication at this time. A dual-chamber rather than single-chamber ICD can be helpful if needing the right atrial lead to start or up-titrate beta-blockers or calcium channel blockers.

Section 7.2: 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy. J Am Coll Cardiol. 2020 Dec, 76 (25) e159–e240

Case 3

Question 3
A. Patients may present with an exacerbation of heart failure with preserved ejection fraction and would benefit from a trial of a low-dose loop diuretic. This can be especially helpful in non-obstructive patients.

Section 8.2: 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy. J Am Coll Cardiol. 2020 Dec, 76 (25) e159–e240

Case 3

Question 4
D. Prescribers should exercise caution when starting or adjusting diuretics since they may exacerbate or worsen LVOT or mid-cavitary gradients.

Section 8.2: 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy. J Am Coll Cardiol. 2020 Dec, 76 (25) e159–e240

Case 3

Question 5
A. The same pathogenic variant is most likely to segregate with family members who also have HCM, even if they have different phenotypes. This is related to variable expressivity. Apical HCM is not thought to be more severe than classic HCM with septal hypertrophy. The variants for both septal or apical hypertrophy are the same.

Section 2.4 and 6.8: 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy. J Am Coll Cardiol. 2020 Dec, 76 (25) e159–e240

HCM With LVOTO and Progressive NYHA Decline

Case 4

Question 1

C. Traditional medical management focuses on the mantra "slow, full, and afterloaded" for managing dynamic LVOTO. Beta blockers and non-dihydropyridine calcium channel blockers (verapamil) are used alone or in combination. Disopyramide has additional bradycardic and anti-inotrophic effects but many patients have a hard time tolerating the anti-cholinergic side effects. Diuretics are typically used sparingly as these hearts are exquisitely sensitive to decreases in preload which can easily exacerbate the degree of LVOTO. Low blood pressure can also exacerbate LVOTO and decrease coronary perfusion pressure given the high LV cavity pressure and elevated EDP. Normotension to mild hypertension should be the goal of medical management. Mavacamten is the first in a new class of myosin inhibiting drugs which work via the anti-inotrope effects.

Ref: ISSN: 0098-7484; 0098-7484, DOI: 10.1016/S0140-6736(21)00763-7

Question 2

E. Patients with HCM are at an increased risk for the development of AFib over their lifetime. Twenty-five percent of patients with HCM will go on to develop AFib. Most patients will be symptomatic but this should be assessed pre-operatively as surgical ablation can be combined with septal reduction surgery. Pulmonary function tests are not required in a never smoker with normal lung sounds. Symptomatic patients do not need provocative testing. Symptomatic patients without LVOT echo gradients at rest or with Valsalva maneuver should undergo provocative testing. Any patient in this age group undergoing cardiac surgery should be screened for obstructive coronary artery disease which would almost certainly be addressed concomitantly.

Ref: ISSN: 1302-8723; 1302-8723

Case 4

Question 3

C. The contribution of SAM to LVOTO can be affected by factors independent of basilar septal hypertrophy and altered flow vectors. Abnormalities in anterior leaflet height (too long), papillary muscles (apically displaced) and accessory chordae from the anterior leaflet directly to the septum are all common findings in patients with HCM. None of these can be specifically addressed with alcohol ablation while all can be addressed at the time of surgery.

Ref: 10.3238/arztebl.2011.0209

Question 4

B. Residual intra-operative LVOT gradients above approximately 30 mmHg usually can be improved upon. One way to address residual SAM is with an Alfieri stitch that ties the mid point of the mitral valve leaflets together. This effectively 'tethers' the mitral valve posteriorly and prevents SAM. Permanent pacemaker placement is usually not indicated in the operating room as lack of normal AV conduction early post-operatively is a frequent finding, and most patients will recover in the first 72 hours after surgery.

Ref: DOI: S0894-7317(19)30975-7 [pii]

Case 4

Question 5

A. The absence of a left bundle branch block following myectomy is likely a marker of an inadequate operation. The left bundle reliably courses through the basilar septum anteriorly and should be surgically interrupted when a myectomy is done. Therefore, its use as a marker of myocardial ischemia is lost. In a patient without other signs of coronary insufficiency, it should be ignored and should not raise clinical concern or lead to work-up or testing.

Ref: DOI: 10.1007/s11748-018-0895-0 [doi]
With your help, patients whose lives have been impacted because of hypertrophic cardiomyopathy (HCM) may be able to reduce symptoms and comorbidities. The American Heart Association is committed to being your resource for diagnosing and treating patients with HCM. Visit the HCM for Professionals webpage for videos, podcasts, clinical review, and tools.