A 33-year-old man presented for evaluation of syncope.

A few weeks earlier, he had become light-headed and developed mild chest discomfort and visual changes while running from home plate to first base during a softball game. A few days before evaluation, he had been running on his treadmill when he became light-headed, lost consciousness, fell, injured his nose, and broke his glasses. Bystanders observed no seizure-like activity. He experienced no bowel or bladder incontinence, tongue biting, or post-event confusion. He denied antecedent palpitations, chest pain, sneezing, coughing, Valsalva maneuver, or change in emotion.

His medical history was remarkable for mild depression and gastroesophageal reflux disease. He was taking 20 mg/d of citalopram and 20 mg/d of pantoprazole. He denied use of illicit drugs or excessive alcohol. His family history was notable for the unexplained death of 3 siblings (at ages 3 days, 1 week, and 3 years) and the unexpected death of his father at age 44 years. No autopsies were performed.

The patient’s cardiac examination demonstrated a regular rhythm with a normal S1/S2, and a soft S4. At rest, no significant murmur was appreciated, but with the Valsalva maneuver a systolic ejection murmur appeared and reached a 3/6 intensity. Otherwise, findings on physical examination were unremarkable.

Results of laboratory tests, including a complete blood cell count and an electrolyte panel, were within normal limits. Electrocardiography (ECG) showed normal sinus rhythm and biatrial enlargement. A 24-hour ambulatory ECG showed no significant atrial or ventricular dysrhythmia despite patient-reported episodes of light-headedness.

1. Which one of the following is the most appropriate next diagnostic test?
   a. Tilt-table testing
   b. Electroencephalography
   c. Transthoracic echocardiography (TTE)
   d. Exercise ECG stress test
   e. Carotid ultrasonography

Although neurocardiogenic syncope can often be detected using tilt-table testing, exertional syncope is not usually due to a vasovagal event. Electroencephalography is a reasonable choice when a generalized seizure is suspected as the cause of syncope, but in this case no convulsive activity or postictal state was reported by event observers. In a patient with exertional syncope, TTE is an appropriate diagnostic test, especially if there is auscultatory evidence of dynamic outflow tract obstruction.1 Exercise ECG stress testing can evaluate for cardiac ischemia but would not be the best next step given the patient’s age and lack of risk factors. Carotid ultrasonography is not the best choice because the patient’s lack of neurologic deficit and young age make a cerebrovascular event an unlikely cause of his syncope.

Evidence of increased ventricular septal thickness (18 mm) with systolic anterior motion of the mitral valve apparatus was noted on TTE. Left ventricular outflow tract (LVOT) obstruction was noted at rest (36 mm Hg) and became severe with the Valsalva maneuver (88 mm Hg). These findings were consistent with a diagnosis of obstructive hypertrophic cardiomyopathy (HCM).

2. Which one of the following is the best initial treatment option for this patient?
   a. β-Blocker
   b. Digoxin
   c. Angiotensin-converting enzyme inhibitor
   d. Long-acting nitrate
   e. Spironolactone

A negative inotropic medication such as a β-blocker or non-dihydropyridine calcium channel blocker would be the most appropriate initial therapeutic intervention. Both β-blockers and calcium channel blockers can decrease the obstructive gradient in HCM by decreasing catecholamine-mediated contractility.2 These agents also increase diastolic filling by decreasing the heart rate. Digoxin is not appropriate in most patients with HCM because it has the opposite effect of a β-blocker, acting as an inotropic agent and increasing LVOT obstruction by increasing contractility. Angiotensin-converting enzyme inhibitors decrease preload and afterload and thus exacerbate the obstructive gradient in HCM. Likewise, diuretics and long-acting nitrates decrease cardiac preload, which also can exacerbate symptoms secondary to outflow tract obstruction. In contrast, patients with HCM should be instructed to avoid dehydration.

The patient was prescribed metoprolol, titrated to 100 mg twice daily. He continued to experience presyncope and...
Hypertrophic cardiomyopathy is a common genetic disorder associated with more than 1000 mutations in 11 genes. It can affect people of all ages and is inherited primarily in an autosomal dominant fashion, although sporadic mutations have been reported. The disease can present with a wide range of clinical manifestations. It has a frequency of 1 in 500 in the general population and is the most common cause of SD in young people. Clinicians must be familiar with the pathophysiology, presenting signs and symptoms, evaluation, and management of HCM. They will often be required to initiate the diagnostic work-up and facilitate management in conjunction with a cardiologist.

Hypertrophic cardiomyopathy is a heterogeneous disorder characterized by myofibril disarray and asymmetric myocardial hypertrophy of the ventricular septum or apex. Most patients have obstruction of the LVOT, which is typically due to systolic anterior motion of the mitral valve leaflets. This can occur at rest or with provocation alone (latent). The symptoms of HCM can also be caused by diastolic dysfunction, mitral regurgitation, and myocardial ischemia.

In patients with HCM, sex is not associated with SD. A first-degree family member with SD is a significant risk factor and should prompt consideration of an implantable cardioverter-defibrillator (ICD). Atrial fibrillation has been associated with inappropriate ICD shocks, but no clear evidence suggests that it is a predictor of SD. It was hoped that the identification of certain genetic mutations would assist in the risk stratification of HCM. Unfortunately, considerable phenotypic variation among patients with genetic mutations has, to date, precluded widespread clinical use for risk stratification in HCM. No clear association has been established between race and SD risk.

Given the patient’s recurrent syncopal episodes, significant LVOT obstruction, and family history of SD, an ICD was implanted for primary prophylaxis.

**DISCUSSION**

**3. Which one of the following therapies would be most appropriate given the patient’s continued symptoms despite maximal medical therapy?**

- a. Heart transplant
- b. Percutaneous alcohol septal ablation
- c. Initiation of amiodarone therapy
- d. Surgical septal myectomy
- e. Dual-chamber pacemaker

Heart transplant would not be indicated at this stage but should be considered in patients with end-stage HCM refractory to medical and surgical therapy. Percutaneous alcohol septal ablation involves administration of ethanol into a septal perforator branch of the left anterior descending coronary artery supplying the involved hypertrophic segment. This causes a controlled myocardial infarction and subsequent atrophy of the obstructing myocardium. Complications from the procedure include infarction of an uninvolved segment or of an undesirable size (due to variations in coronary anatomy and distribution) and a relatively high incidence of complete heart block. Because of these potential complications and the lack of long-term follow-up, alcohol ablation is not considered the primary therapy for medically refractory HCM. Amiodarone would not be indicated in the absence of atrial fibrillation or ventricular arrhythmia. Surgical septal myectomy is the primary treatment option for symptomatic HCM refractory to medical therapy. Dual-chamber pacemakers have been used for drug-refractory, symptomatic HCM. However, they are not the primary treatment option, and their efficacy has been disputed in clinical trials.

**4. Which one of the following is an established major risk factor for sudden death (SD) in patients with HCM?**

- a. Male sex
- b. First-degree family member with a history of SD
- c. Atrial fibrillation (AF)
- d. Presence of established HCM-associated gene mutation
- e. European ancestry

In patients with HCM, sex is not associated with SD. A first-degree family member with SD is a significant risk factor and should prompt consideration of an implantable cardioverter-defibrillator (ICD). Atrial fibrillation has been associated with inappropriate ICD shocks, but no clear evidence suggests that it is a predictor of SD. It was hoped that the identification of certain genetic mutations would assist in the risk stratification of HCM. Unfortunately, considerable phenotypic variation among patients
Suspection for HCM is often predicated on a patient’s symptoms, physical examination findings, family history of SD, or left ventricular hypertrophy (LVH) on ECG. Symptoms, which vary with the underlying mechanism, include exertional dyspnea, dizziness, presyncope, syncope, chest pain (anginal or nonanginal), and/or palpitations. Physical examination may include a sustained left ventricular (LV) impulse, a systolic heart murmur, an S4, a bifid carotid upstroke, and a “spike and dome” arterial pulse.2

The systolic murmur in patients with HCM is typically due to LVOT obstruction and/or mitral regurgitation. The LVOT murmur is usually located at the left sternal border, has a harsh quality, and may be present at rest or only with provocation. Maneuvers are helpful in differentiating the murmur of obstructive HCM from aortic stenosis and benign, systolic “flow” murmurs. The murmur of obstructive HCM increases with decreased preload or decreased afterload and decreases under opposite conditions. It increases with squat-to-stand and Valsalva maneuvers (due to decrease in preload at strain phase) and decreases with stand-to-squat or handgrip maneuvers.

Suspected HCM should be confirmed with TTE. Findings characteristic of HCM include asymmetric LVH, an LV wall thickness of 15 mm or greater in patients without another cardiac or systemic cause, and LVOT obstruction on Doppler ultrasonography.2,3 Although the most common form of HCM is associated with asymmetric LVH, symmetric LVH does not exclude HCM. In patients without resting outflow tract obstruction (gradient <30 mm Hg), provocative maneuvers such as Valsalva, exercise, or administration of amyl nitrite should be performed.2 Ambulatory 24-hour ECG monitoring should be performed to evaluate for asymptomatic supraventricular or ventricular arrhythmias.

Additional tests to be considered for risk stratification include baseline ECG and exercise testing. Exercise testing is helpful in the assessment of symptoms, blood pressure response to exercise, arrhythmias, myocardial ischemia, and prognosis.9 When coupled with TTE, exercise testing can be helpful in assessing for latent LVOT obstruction. Genetic testing can be helpful in identifying affected family members and providing adjunctive prognostic information.9 Genetic testing is currently not routinely used to make the diagnosis because several suspected genetic mutations have yet to be identified and penetrance in patients with gene mutations is variable.2

The clinical course of patients with HCM varies and depends on multiple factors. Initial HCM patient cohorts were limited by referral bias and reported an ominous annual mortality rate of 3% to 6%. In more recent reports, however, the mortality rate is about 1%, which is similar to that of the general adult US population.3 The aims for management of HCM are to minimize symptoms, reduce SD risk, limit progression of disease, and manage associated complications, such as AF or heart failure.

Medications are the initial treatment for symptoms of HCM. β-Blockers are the mainstay drug and are particularly efficacious in the relief of exertional symptoms. In patients who experience considerable adverse effects with β-blockers or in whom they are contraindicated, verapamil should be considered.10 The beneficial effects of these medications may be mediated by a decrease in heart rate (which increases diastolic filling) and negative-inotropic effects (which decrease myocardial oxygen demand and decrease contractility, thereby improving the LVOT gradient).1 In patients with persistent symptoms while receiving treatment with a β-blocker or verapamil, disopyramide can be considered. It is less frequently used, however, because of its anticholinergic adverse effects and potential proarrhythmic effects.3

Dual-chamber pacing has been used in drug-refractory HCM. Right-ventricular pacing with a short atrioventricular delay results in dyssynchronous LV contraction and reduces LVOT obstruction.10 A double-blinded randomized controlled trial showed minimal reduction in LVOT obstruction and no improvement in quality of life with pacing, except in patients older than 65 years.3 Despite mixed clinical data, it remains a class IIb recommendation for symptomatic patients with medically refractory HCM and substantial LVOT obstruction at rest or with provocation.5

Invasive modification of the ventricular myocardium is the preferred approach in patients with drug-refractory HCM with marked obstruction. Surgical myectomy, the mainstay treatment, can be used in both septal and apical-predominant HCM, resulting in a persistent improvement in symptoms, exercise capacity, and long-term survival.3,10

Percutaneous alcohol septal ablation is an alternative approach in which ethanol is injected into a septal perforator branch of the left anterior descending coronary artery, inducing a controlled myocardial infarction. Potential complications of this method include creation of a substrate for ventricular arrhythmias, a larger infarction than desired, complete heart block necessitating pacemaker placement, and a ventricular septal defect. In the absence of a randomized controlled trial comparing the 2 approaches, surgical myectomy remains the preferred treatment because of its proven effectiveness in symptom relief and the presence of long-term follow-up data substantiating it as a robust treatment with a low complication rate. Alcohol ablation is an alternative in drug-refractory patients who are at increased operative risk or who have no access to or refuse surgical myectomy.2,4

Sudden death in HCM is caused by sustained ventricular tachycardia or ventricular fibrillation. It typically occurs in patients younger than 35 years, although it can also occur in older patients.3 The major risk factors for SD are previous cardiac arrest or spontaneous sustained ventricular
tachycardia, a family history of HCM-related SD in a close relative or multiple family members, unexplained syncope, nonsustained ventricular tachycardia, abnormal blood pressure response during exercise, and extreme LVH (LV wall thickness >30 mm). Although certain gene mutations are associated with increased risk for SD, genetic testing is not recommended in risk stratification for ICD implantation. A minor risk factor for SD is LVOT obstruction.

Patients with HCM are advised against participation in intense competitive sports, other forms of “burst” activity, and systematic isometric exercise (heavy lifting) that may increase their risk of SD. No evidence suggests that prophylactic verapamil, disopyramide, or β-blockers reduce the risk of SD. Amiodarone has been associated with improved survival in HCM, but toxicity limits its use.

An ICD is the mainstay therapy for SD prevention and is a class I indication for secondary prevention in patients with a history of ventricular fibrillation or hemodynamically unstable ventricular tachycardia. The indications for ICD as primary prevention in HCM remain a subject of debate because of the variable positive predictive value of each risk factor. Physician discretion is thus important in considering an ICD for primary prophylaxis. In general, ICD implantation is reasonable in patients with HCM and at least 1 major risk factor (class IIa recommendation).

Atrial fibrillation can occur in 20% to 25% of patients with HCM. Increased LV diastolic pressure and heart failure can result in left atrial enlargement, remodeling, and AF. Atrial fibrillation is associated with increased morbidity and mortality in HCM due to loss of active diastolic LV filling (atrial “kick”) and decreased diastolic filling time with a rapid ventricular rate. Thus, in addition to rate control and consideration of anticoagulation to reduce stroke risk, maintenance of sinus rhythm is preferred. This can be achieved pharmacologically with amiodarone or by radiofrequency ablation. Screening and treatment of sleep-disordered breathing is also recommended in patients with HCM because of the increased incidence of AF in this population.

An understanding of the pathophysiology of HCM is critical in managing severe illnesses in patients with HCM. A decrease in preload or afterload can lead to increased obstructive gradient through the LVOT and an increase in heart rate worsens impaired diastolic filling, all of which can be detrimental to cardiac output in patients with obstructive HCM; thus, caution is advised when using diuretics, vasodilators, and inotropic agents in these patients.

Family members of patients with HCM should be screened. Genetic consultation is helpful in identifying the pattern of inheritance and determining whether to proceed with genetic testing. In patients with an identified genetic mutation, family members can be screened for the mutation of interest. If no mutation has been identified, first-degree family members should be screened with a history and physical examination, 12-lead ECG, and TTE. Such screening should occur every 12 to 18 months for family members aged 12 to 18 years and at least every 5 years for those who are older.

Follow-up of patients with HCM depends on the clinical circumstances. Patients should be seen for a history and physical examination at least annually. They should undergo regular 24-hour ambulatory ECG monitoring and TTE because the risk profile for SD may change with time.

Hypertrophic cardiomyopathy is a common disorder encountered in a variety of clinical settings and may present with a systolic heart murmur, symptoms, LVH on ECG, or a family history of SD. Clinicians’ understanding of the pathophysiology of HCM is critical to facilitate optimal diagnosis and management while avoiding potentially detrimental therapies. Patients should undergo risk stratification for SD and have an ICD implanted if indicated. The initial treatment of symptoms is a β-blocker. Surgical myectomy should be considered in patients with significant outflow obstruction and drug-refractory symptoms.

REFERENCES
1. Strickberger SA, Benson DW, Biagioli I, et al. AHA/ACCF Scientific Statement on the evaluation of syncope: from the American Heart Association Councils on Clinical Cardiology, Cardiovascular Nursing, Cardiovascular Disease in the Young, and Stroke, and the Quality of Care and Outcomes Research Interdisciplinary Working Group; and the American College of Cardiology Foundation: in collaboration with the Heart Rhythm Society. Circulation. 2006;113(2):316-327.

Correct answers: 1. c, 2. a, 3. d, 4. b, 5. e