BMJ Best Practice

Hypertrophic cardiomyopathy

Straight to the point of care

Last updated: Mar 21, 2024

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Summary

Hypertrophic cardiomyopathy (HCM) is the most common cardiomyopathy and the most frequent cause of sudden cardiac death in young people.

Presentation varies from asymptomatic to symptoms of heart failure.

Physical examination may be normal at rest. Auscultation along the left sternal border when the patient is standing after a brief period of exercise may elicit a murmur.

Family history may be present. Echocardiography should be used to screen first-degree family members.

Has a benign prognosis in the majority of patients.

Medical therapy with beta-blockers, calcium-channel blockers, or disopyramide is used in symptomatic patients.

A subset of patients with increased risk for sudden death should undergo defibrillator implantation.

Definition

HCM is a genetic disorder characterised by left ventricular hypertrophy that is not solely explained by abnormal loading conditions.[1] It is the most common genetic heart disease, as well as the most frequent cause of sudden cardiac death in young people.[2] Given its prevalence in younger patients, HCM is frequently confused with athlete's heart. In older patients, HCM may be misdiagnosed as hypertensive heart disease. Many patients will have no symptoms at the time of diagnosis and will be diagnosed following routine examination or family screening of an affected family member.[1] [2]

Epidemiology

Hypertrophic cardiomyopathy (HCM) is estimated to affect 15-20 million people worldwide and is the most common cause of sudden death in children and young adults.[6] [7] [8] It is estimated to affect 1 in 500 adults, although population-based genetic studies suggest the condition is more common than reported, with the prevalence of HCM gene carriers estimated at 1 in 200 people or greater.[2] [8] [9]

The mean age of presentation differs among published series but in a large community sampling it was noted to be 57 on average (range 16 to 87 years).[10]

While the disease is autosomal dominant with no known sex predilection, women are more likely to evade diagnosis, presenting at an older age with a greater likelihood of New York Heart Association class III/IV symptomatology at the time of diagnosis.[11] Sudden death is most common in young patients, and death from heart failure or stroke occurs more frequently in middle age and beyond.[12]

While the disease can affect all ethnic groups, apical HCM is seen much more commonly in Asian people. Apical HCM accounts for <5% of HCM cases in non-Asian people and 15% to 40% of cases in Asian people.[13] [14]

Aetiology

Hypertrophic cardiomyopathy (HCM) is a genetic disease of the cardiac sarcomere, caused by mutations in genes that encode different components of the contractile apparatus.[15] The disease is genetically heterogeneous, with over 270 identified mutations in 13 causative genes.[16] [17] Mutations in the beta-cardiac myosin heavy chain are the most common (44% of mutations), with mutations in the myosin binding protein C gene second in frequency (35% of mutations).[17] Mutations in the troponin I, troponin T, and alpha-tropomyosin genes account for 10% to 15% of mutations.[17] Up to 5% of patients may have more than one mutation.[18] Phenotypic expression of disease is heterogeneous even within families with the same genetic defect.[4] The overall yield of genetic testing is low in HCM, with no causative gene identified in approximately 50% of patients.[19]

Pathophysiology

Presence of one of the responsible genetic mutations leads to septal thickening from myocyte hypertrophy as well as abnormal, thickened, disorganised collagen matrix. Septal hypertrophy may be diffuse or localised to one particular location of the septum. In the most classic form, hypertrophy is most marked in the septum immediately below the aortic valve.[4] The hypertrophied septum may lead to left ventricular (LV) outflow tract obstruction, either in isolation or in association with systolic anterior motion of the mitral valve.[4] Systolic anterior motion of the mitral valve occurs in response to turbulent flow in the subaortic region wherein the anterior leaflet of the mitral valve is pulled into the subaortic region, thereby leading to further obstruction.

Obstruction may alternatively be confined to the mid-cavity of the left ventricle. This occurs as a result of mid-septal hypertrophy and hypertrophy of the LV papillary muscles. Patients develop intracavitary systolic obstruction secondary to apposition of the septum and the papillary muscles. These patients typically do not have systolic anterior motion of the mitral valve as the obstruction is lower in the ventricular cavity. Isolated hypertrophy of the apex may also occur (apical HCM).[4] Increased obstruction will occur in response to an increase in heart rate, myocardial contractility, reduced ventricular volume, and peripheral vasodilation. Most patients demonstrate impaired diastolic relaxation irrespective of the presence of hypertrophy.[4] Diastolic

dysfunction leads to increased filling pressures and is argued to be the primary source of symptoms in many patients, particularly young people.[4] [20]

Myocardial ischaemia is common and likely to be multifactorial in origin. It may be due to increased myocardial oxygen demand and reduced myocardial capillary density relative to the LV hypertrophy, small vessel disease, compression of septal perforating arteries, myocardial bridging (characterised by a segment of a major epicardial coronary artery tunnelling through the myocardium), obstruction to LV outflow, and increased coronary vascular resistance due to abnormal LV relaxation and impaired filling.[4] The presence of symptoms may be due to the degree of subaortic stenosis at rest and with exercise, impaired diastolic relaxation, arrhythmias, impaired systolic contraction in the absence of obstruction, and ischaemia.[4]

Classification

Obstructive versus non-obstructive

Disease is classified as obstructive or non-obstructive based on the presence or absence of left ventricular outflow tract obstruction on echocardiography at rest.[1] [2] A resting pressure gradient between the left ventricle and the aorta is present in 37% of patients. An additional 33% will have provocable obstruction (e.g., obstruction with exercise), such that the majority of patients have some degree of obstruction.[3] There is not a strong correlation between symptoms and the degree of obstruction and, in fact, patients with severe obstruction may be asymptomatic.[4]

Site of obstruction

Patients may be classified based on the site of maximal left ventricular obstruction:[4]

- Subaortic obstruction (classic)
- Mid-ventricular obstructive HCM
- Apical HCM
- Complex obstructive HCM

Some patients may also have co-existing right ventricular (RV) obstruction. The incidence of RV systolic obstruction in HCM has been reported as 15% to 92% by catheterisation studies.[5]

Case history

Case history #1

A 21-year-old active college student with no past medical history has sudden loss of consciousness 1 hour into a game of basketball. CPR is administered by bystanders. On the arrival of an emergency medical professional, he regains consciousness. The family history is significant for a murmur in his father and paternal grandmother. Physical examination reveals a systolic ejection murmur that increases in intensity when going from a supine to standing position and disappears with squatting.

Case history #2

A 60-year-old woman presents with progressive dyspnoea on exertion over the last 2 months. She is otherwise well, with no risk factors for ischaemic heart disease. Family history is significant for a cousin who died suddenly in his youth, but is otherwise unremarkable. Physical examination reveals a prominent jugular a-wave and a double apical impulse. There are no murmurs audible. An S4 is present. The remainder of the examination is normal.

Other presentations

Other common symptoms include: chest pain, palpitations, postural light-headedness, resuscitated sudden death, and fatigue.[4] Patients may remain asymptomatic and be diagnosed solely on the basis of family screening. Diagnosis may also occur as a consequence of incidental findings (e.g., an abnormal ECG in the context of community or work-related medical check-ups or sports pre-participation screening; the incidental detection of a murmur; or increasingly, genotype-first identification as a result of secondary findings during research or clinical sequencing for other indications).

In secondary and tertiary care, patients with hypertrophic cardiomyopathy may present to the heart failure clinic with symptoms of heart failure; the arrhythmia clinic with early-onset conduction disease, atrial arrhythmia, or ventricular arrhythmia; or the emergency department with suspected myocarditis.[1]

Approach

In suspected cases, an evaluation with history (including family history, physical examination), ECG, and echocardiography should be performed. The latter establishes the diagnosis. Asymptomatic patients are usually diagnosed at the time of routine heart examination or family screening.[1][4] Patients are most commonly diagnosed after the onset of clinical manifestations, however, with only 32% of patients diagnosed on routine medical evaluation.[21] Laboratory DNA analysis for mutant genes is the most definitive method for establishing the diagnosis of hypertrophic cardiomyopathy (HCM), but is usually used only for screening purposes.

History

Family history

A family history of syncope, heart failure, or sudden or premature death should be taken. Sudden cardiac deaths may sometimes have been reported as accidental deaths, for example, drowning or unexplained traffic accidents.[1] Other points to note in the family history include cardiac transplantation, pacemaker and defibrillator implants, and features suggestive of systemic disease (e.g., stroke at a young age, skeletal muscle weakness, or renal disease). A three- to four-generation family pedigree should be created to aid in diagnosis, provide clues to aetiology, determine inheritance pattern, and identify at-risk relatives.[1] Sarcomeric HCM is autosomal dominant and is therefore characterised by the presence of affected individuals across generations, with transmission from parents of either sex and a 50% risk of allele transmission to offspring. Family history may be negative, however, as the disease has incomplete penetrance.[1]

Symptoms

Patients may be symptom-free. However, it is important to note any symptoms of pre-syncope or syncope, particularly when occurring with exercise, dyspnoea on exertion, palpitations, or chest pain. Patients over 50 years of age may present with atrial fibrillation or symptoms of a stroke.[22]

Physical examination

Examination may be remarkable for a left ventricular (LV) lift; a double apical impulse; a brisk carotid upstroke; a systolic ejection murmur at the lower left edge that is accentuated by exercise and standing and lessened by lying supine or squatting; and a fourth heart sound.[4]

Diagnostic testing

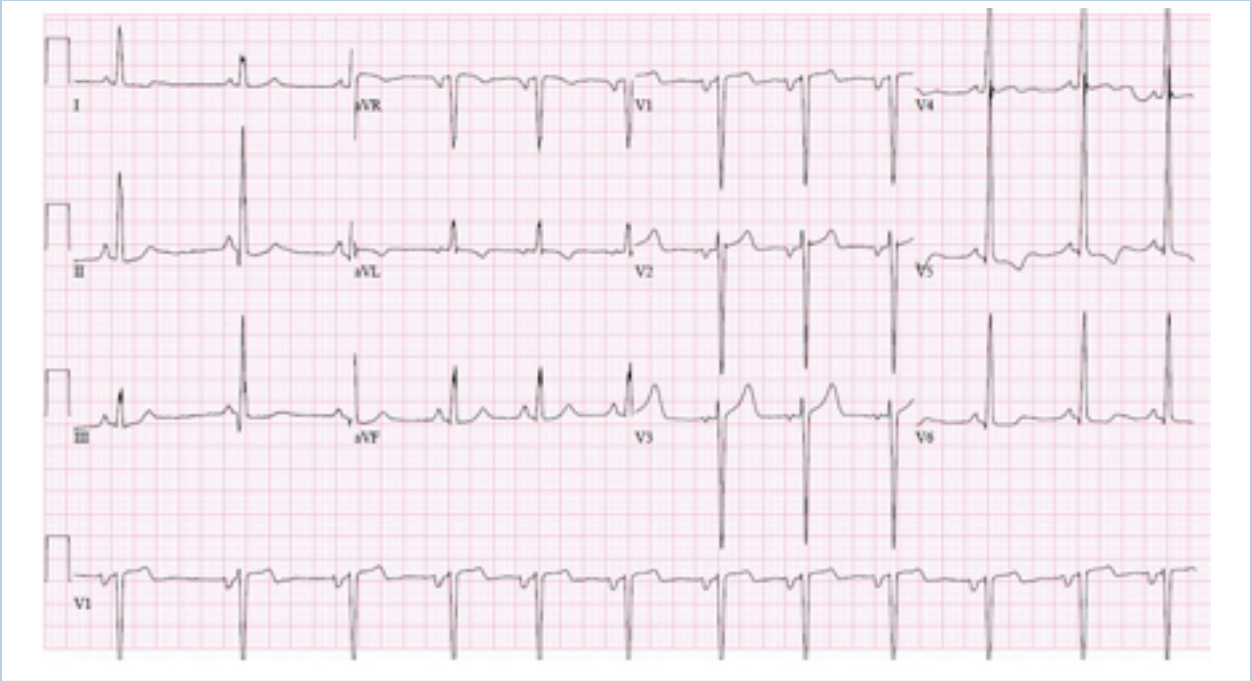
ECG

A resting 12-lead ECG is recommended at the first clinic visit in all individuals with known or suspected HCM and should be repeated whenever there is a change in symptoms in patients with an established diagnosis.[1] Most patients have ECG abnormalities; these are not specific to HCM, but rather, should prompt further investigation with echocardiography. An abnormal ECG may predate the finding of hypertrophy on echocardiography.[23]

- Repolarisation abnormalities are common. T-wave inversion commonly involves the inferior and lateral leads and T waves are deep and often preceded by ST-segment depression.[24] Deeply inverted T waves in the precordial leads are suggestive of apical HCM.[25]

- Prominent abnormal Q waves may be seen in the inferior (II, III, aVF) and/or lateral (I, aVL, V5-6) leads, reflecting septal hypertrophy.[25]
- Increased QRS voltages indicating left ventricular hypertrophy (LVH) may be present. These are nearly always associated with other ECG abnormalities in HCM.[24] The presence of isolated QRS voltage criteria for LVH in the absence of other ECG markers is present in fewer than 2% of patients with HCM.[26]
- ECG signs of left and right atrial enlargement and P-wave prolongation (a known predictor of atrial fibrillation) may be observed. They rarely occur in isolation; other ECG abnormalities such as repolarisation changes or signs of LVH are generally present. Left atrial enlargement reflects diastolic dysfunction, high filling pressures, outflow obstruction, and functional mitral regurgitation. Left atrial dilatation and dysfunction are markers of adverse prognosis.[24]
- Left axis deviation (caused by LVH) and ventricular pre-excitation may also be seen.[24]
- Some patients may present with arrhythmias, for example, atrial fibrillation or supraventricular tachycardia.[24]

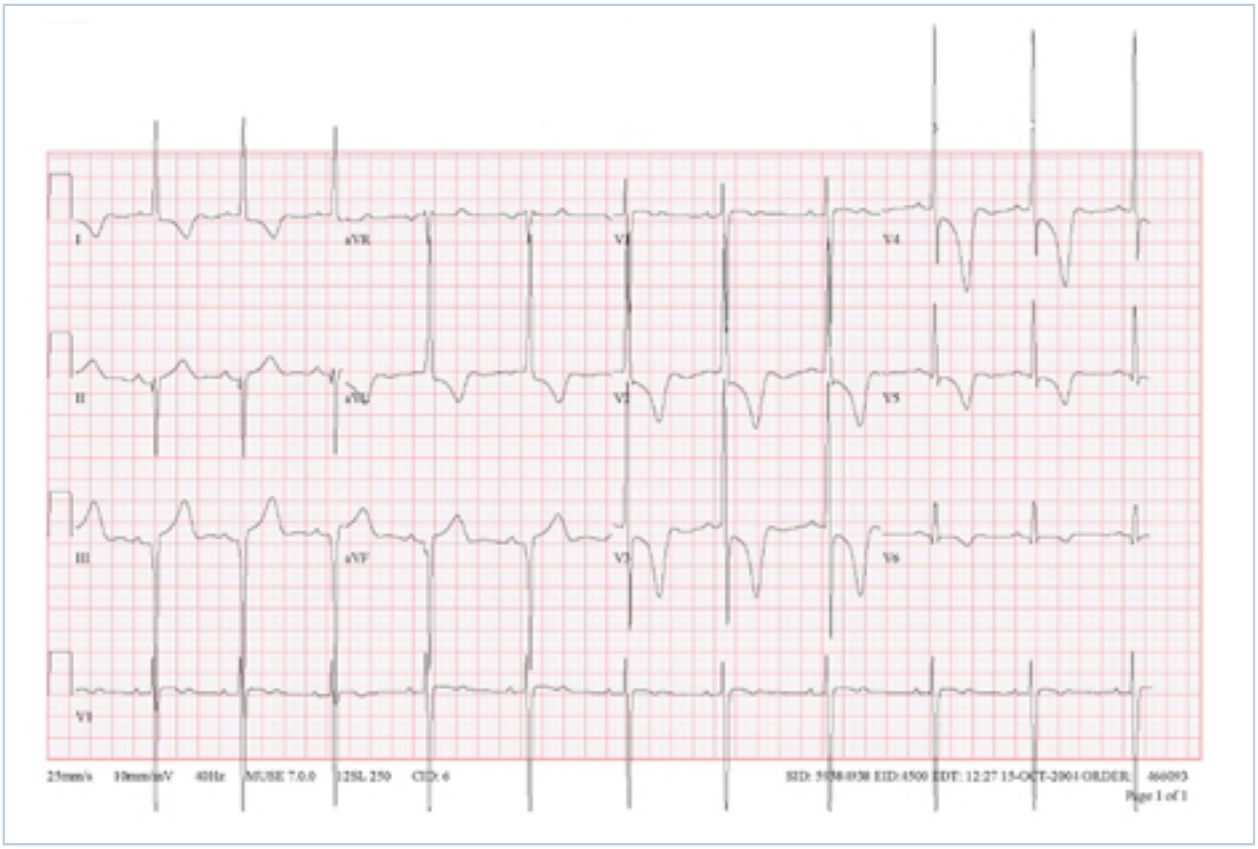
The ECG is normal in only a small proportion (5% to 10%) of patients at presentation.[1] [25] These patients have been reported to have a more favourable clinical course than those with ECG abnormalities.[26]



ECG showing changes associated with LVH

From the collection of Melanie Everitt MD, Heart Failure & Transplantation Program, Primary Children's Medical Center, Salt Lake City, UT; used with permission

DIAGNOSIS



Giant T-wave inversion

From the collection of Dr Anji T. Yetman MD, University of Utah

Laboratory tests

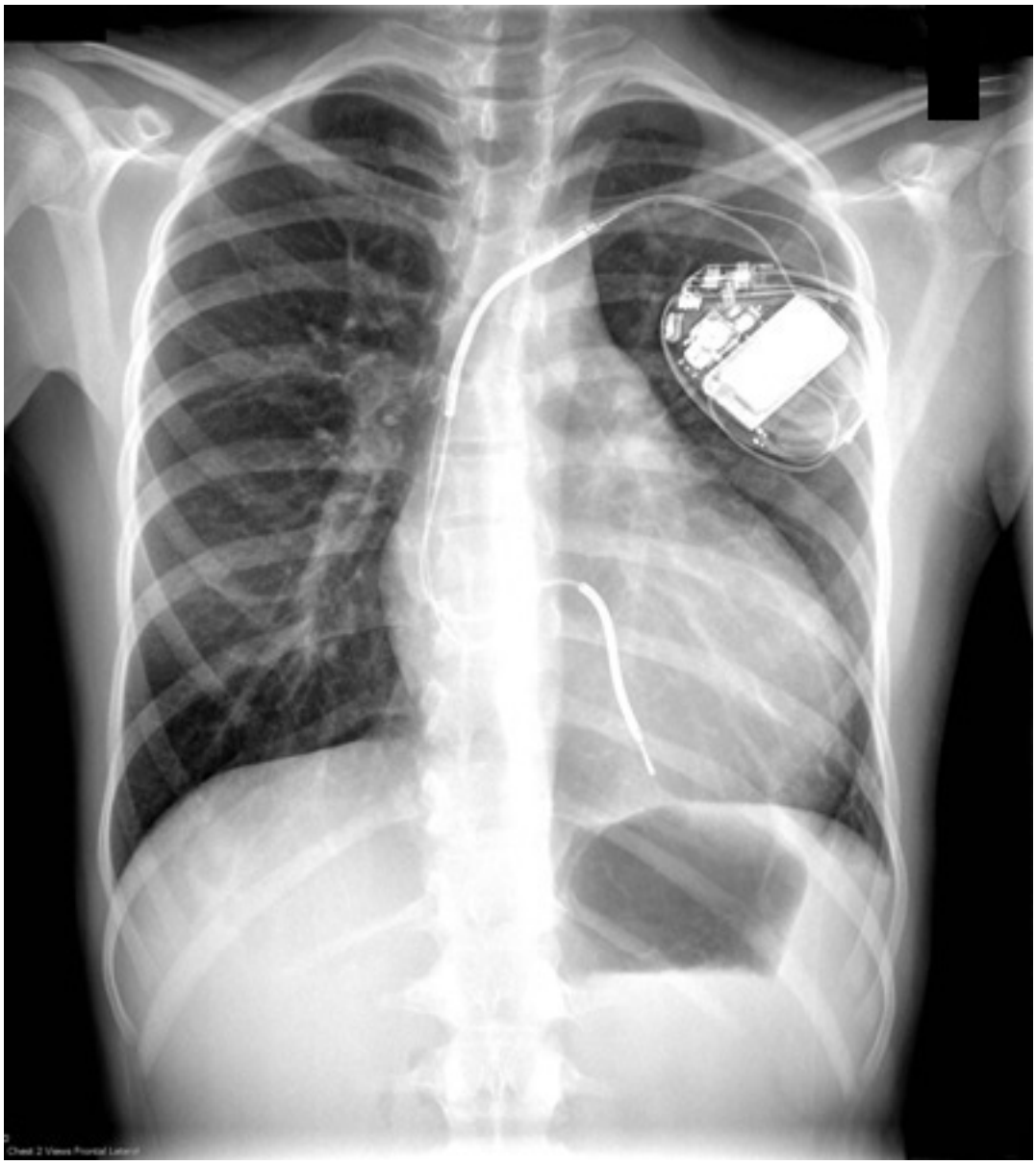
US guidelines do not recommend laboratory tests as part of the initial work-up.[2] However, European guidelines recommend that all patients with suspected or confirmed HCM should have routine laboratory tests done to establish aetiology, assess disease severity, and aid in the detection of extracardiac manifestations and assessment of secondary organ dysfunction. The following first-line tests are recommended:[1]

- Creatine kinase (CK): raised levels are a useful clue when trying to establish aetiology; metabolic disorders such as Danon or mitochondrial disease, which can mimic HCM, should be considered. When CK is persistently raised, a detailed examination by a neurologist should be considered.
- Liver function tests: liver dysfunction is prevalent in patients with chronic heart failure. Abnormal liver function tests can also be a useful clue when trying to establish aetiology; metabolic disorders such as Danon disease, which can mimic HCM, should be considered.
- Renal function: impaired renal function may be seen with severe LV dysfunction.
- N-terminal pro-brain natriuretic peptide (NT-proBNP): high levels are associated with cardiovascular events, heart failure, and death, and may have diagnostic, prognostic, and therapeutic monitoring value.
- Troponin: higher levels are associated with a higher risk of cardiovascular events, heart failure, and death, and may have diagnostic, prognostic, and therapeutic monitoring value.
- Urinalysis; proteinuria is suggestive of renal impairment.

Following specialist evaluation, additional tests to detect rare metabolic and syndromic causes are often required in patients with cardiomyopathy and extracardiac features.[1]

Chest x-ray

A chest x-ray may show cardiomegaly secondary to LVH or left atrial enlargement, or may be normal.[4] This test is not particularly sensitive.



CXR of a patient with HCM demonstrating cardiomegaly

From the collection of Melanie Everitt MD, Heart Failure & Transplantation Program, Primary Children's Medical Center, Salt Lake City, UT; used with permission

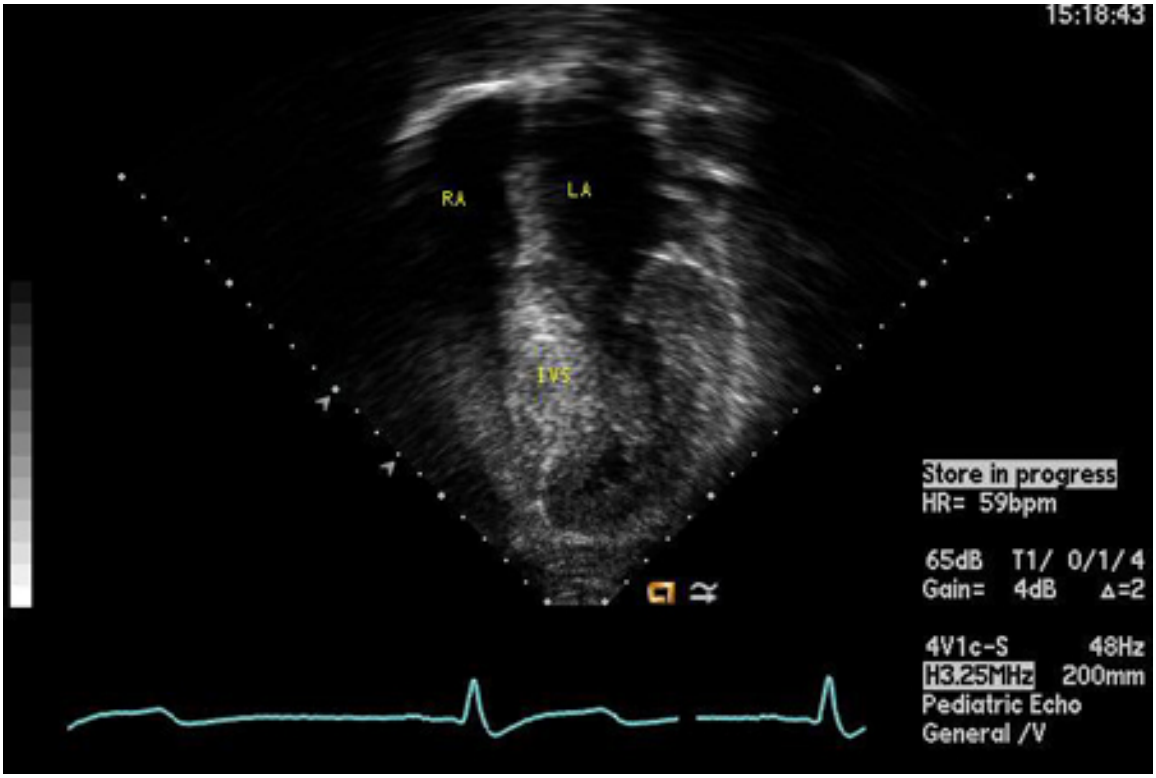
Transthoracic echocardiography

At initial assessment of all patients with HCM, transthoracic 2D and Doppler echocardiography are recommended. The classic finding is LVH, typically asymmetric hypertrophy of the septum.[4] [27] Echocardiography is also used for family screening of an affected person, and for risk assessment of sudden cardiac death (SCD) in patients with a known diagnosis of HCM.

- Clinical diagnosis of HCM is confirmed when maximal end-diastolic wall thickness ≥15 mm is imaged anywhere in the left ventricle (LV). More limited hypertrophy (≥13 mm) can be diagnostic

when present in family members of a patient with HCM or in conjunction with a positive genetic test.[2] [27]

- Systolic anterior motion of the mitral valve may also be seen, along with mitral insufficiency.[2]
- LV outflow tract obstruction (LVOTO) may be present. By convention, LVOTO is defined as a peak instantaneous Doppler LV outflow tract gradient of ≥30 mmHg, but the threshold for invasive treatment is usually considered to be ≥50 mmHg.[1]
- There may be abnormalities of diastolic function (present in 80% of patients independent of the presence of LVOTO).[2] Diastolic dysfunction should be assessed by Doppler tissue imaging as part of the echocardiographical screening test of first-degree relatives, as this abnormality may precede the onset of overt LVH.[27] [28]



Apical 4-chamber image demonstrating hypertrophy of the interventricular septum

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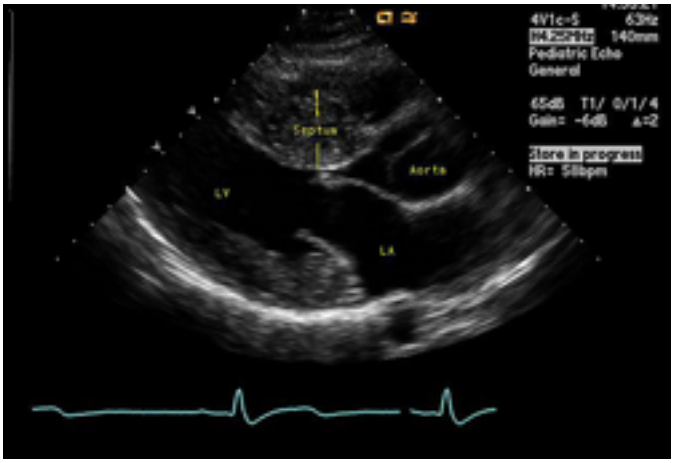

Long axis echocardiography view - asymmetrical septal hypertrophy

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Other types of echocardiography

- Stress echocardiography can be helpful in selected patients to evaluate myocardial ischaemia.[1]
- Exercise echocardiography is useful to identify provocable LVOTO and exercise-induced mitral regurgitation in symptomatic patients with HCM.[1]
- Trans-oesophageal echocardiography is limited to select indications, such as the exclusion of atrial thrombi related to atrial fibrillation, investigating the method of obstruction in patients with LVOTO where this is not obvious, elucidating the mechanism of mitral regurgitation, or planning invasive interventions such as septal myectomy.[1]

Exercise ECG

Exercise testing is performed to aid in risk stratification. Abnormalities associated with an increased risk of SCD include abnormal blunted systolic BP response of <20 mmHg to exercise, ventricular arrhythmias, progressive ST depression, and symptoms.[29] [30]

Holter monitoring

This may be normal or demonstrate ventricular or supraventricular arrhythmias. Ventricular arrhythmias are associated with an increased risk of sudden death.[25]

Nuclear medicine techniques

Patients with exertional chest pain or ventricular tachycardia on Holter monitoring should undergo nuclear testing with either single-photon-emission computed tomography or positron emission tomography.[27] Myocardial perfusion imaging may demonstrate perfusion defects even in the absence of obstructive lesions.[2] Patients may have fixed or reversible defects. Patients with reversible defects should undergo cardiac catheterisation to identify possible causes of ischaemia.

Nuclear medicine can also play a role in diagnosis; it is particularly helpful in the aetiological diagnosis of cardiac amyloidosis.[1]

Cardiac magnetic resonance (CMR)

Contrast-enhanced CMR can be a useful adjunct in patients with HCM at initial evaluation.[1] [2] It can aid diagnosis and contribute to risk stratification and management.

- LV wall thickness can be assessed; the use of CMR may thus increase the diagnostic yield in patients with suspected HCM who have poor visualisation by echocardiogram of the LV walls or apex.[1] [2] [27]
- Systolic and diastolic function can also be assessed, as well as mitral valve function, LVOTO, and left atrial dimensions.[1]
- The use of late gadolinium enhancement techniques can identify areas of myocardial fibrosis that may be a marker for adverse outcomes, or may aid in differentiating HCM from an athletic heart.[31]
- CMR is also emerging as a means of identifying patients who are at increased risk for arrhythmias. Several studies have found the presence of myocardial fibrosis by late gadolinium enhancement to be associated with the occurrence of ventricular arrhythmias, as well as an independent risk factor for death.[2] [32] [33] [34] [35] [36] [37]
- Tissue characterisation on CMR can provide clues regarding aetiology, as characteristic findings are associated with certain diseases, for example, in sarcomeric HCM, a patchy mid-wall in hypertrophied areas is typical, while in amyloidosis-related cardiac hypertrophy, diffuse subendocardial late gadolinium enhancement is seen. These findings should be assessed collectively with genetic results and other clinical features by operators expert in cardiac imaging and the evaluation of heart muscle disease.[1]

  Serial follow-up CMR, every 2-5 years depending on initial severity and clinical course, can assist in evaluating disease progression as well as the benefits of therapy.[1]

Cardiac computed tomography (CT)

Although not used commonly, CT can provide important insights when echocardiography is technically limited and CMR imaging is contraindicated or unavailable.[2] Cardiac CT provides clear definition of LV structure (including hypertrophy pattern, wall thickness measurement, detection of subaortic membrane, and intracardiac thrombus) and function. Disadvantages of CT are the use of radiation and radioiodine contrast and inferior temporal resolution compared with echocardiography.[2]

CT coronary angiography

Indicated in patients with exertional chest pain or ischaemia on nuclear testing to check for the presence of concomitant coronary artery disease or myocardial bridging, comorbidities which can affect the clinical manifestations and course of HCM.[1] [2] [27]

Cardiac catheterisation

In symptomatic patients with HCM and inconclusive non-invasive cardiac imaging, left and right heart catheterisation may be considered to assess the severity of LVOTO and to measure LV filling pressures.[1] [2] It can also be used to check for the presence of concomitant coronary disease or myocardial bridging, and is recommended for patients who are candidates for septal reduction therapy.[2]

Endomyocardial biopsy

Endomyocardial biopsy is not usually recommended for diagnosis of HCM but may be considered on rare occasions, especially when the pattern of hypertrophy is diffuse and there is suspicion for other cardiomyopathies presenting with hypertrophy.[1]

Risk stratification

Risk of sudden cardiac death (SCD)

After diagnosis, patients should undergo risk stratification including Holter monitoring and exercise ECG, unless contraindicated, to further define their risk of sudden death.[2]

The European Society of Cardiology (ESC) has developed a risk prediction calculator for SCD at 5 years in patients ≥16 years with HCM.[38] Risk calculation is based on age, maximal LV wall thickness, left atrial diameter, LV outflow tract gradient, family history of SCD, non-sustained ventricular tachycardia, and unexplained syncope. Risk of SCD should be re-evaluated at 1-2 year intervals or whenever there is a change in clinical status.[1] These models should not be used in elite athletes or in individuals with metabolic/infiltrative diseases (e.g., Anderson-Fabry disease) and syndromes (e.g., Noonan syndrome).[1]

It should be noted that current risk-stratification models may be unreliable in the prediction of future sudden death, and implantable cardioverter-defibrillator (ICD) placement may still be warranted in HCM patients with low-risk scores.[39] US guidelines reflect this uncertainty, recommending that the tool be used as an aid to the shared decision-making process for ICD placement in patients with clinical risk markers, whereas European guidelines recommend that it should be used as the basis of decision-making for all patients with HCM.[1] [2]

ESC guidelines recommend that implantation of an ICD should be considered in patients with an estimated 5-year risk of sudden death of ≥6%, following detailed clinical assessment that considers: (i) the lifelong risk of complications; (ii) competing mortality risk from the disease and comorbidities; AND (iii) the impact of an ICD on lifestyle, socio-economic status, and psychological health. It may also be considered in patients with a risk between ≥4% and <6% on an individual basis. For patients who are in the low-risk category (<4% estimated 5-year risk of SCD), ICD is generally not recommended. However, the guidelines acknowledge that ICD may be considered in low-risk patients who have extensive late gadolinium enhancement (≥15%) on CMR or LV ejection fraction <50%; these factors do not form part of the HCM risk-SCD, but evidence suggests that they increase the risk of SCD. Shared decision-making is recommended.[1]

Risk factors for SCD are as follows:[1] [2] [40]

- Younger age: some studies have reported a significantly increased risk of SCD in younger patients.
- Non-sustained ventricular tachycardia (defined as ≥3 consecutive ventricular beats at ≥120 beats per minute lasting <30 seconds) on Holter monitor: occurs in 20% to 30% of patients.
- Abnormal blood pressure (BP) response to exercise: defined as a rise in systolic BP of <20 mmHg, no rise, or a fall in BP of >20 mmHg during exercise. Medications may affect the BP response and should be considered in the interpretation of exercise test results.
- Massive hypertrophy (LV wall thickness ≥30 mm).
- Severe LVOTO by echocardiogram (LVOTO >30 to 50 mmHg): while severe obstruction is considered a minor risk factor for sudden death, the degree of outflow tract obstruction generally does not correlate with the risk of sudden death. Medical therapy or surgery to decrease outflow tract obstruction does not decrease the risk of sudden death.
- Family history of sudden death: while definitions vary, a family history of SCD is usually considered clinically significant when one or more first-degree relatives have died suddenly aged <40 years

with or without a diagnosis of HCM, or when SCD has occurred in a first-degree relative at any age with an established diagnosis of HCM.
- Personal history of unexplained syncope.
- Prior cardiac arrest, or sustained ventricular tachycardia.
- LV systolic dysfunction with ejection fraction <50%.
- Left atrial enlargement.
- Presence of LV apical aneurysm.
- Diffuse and extensive late gadolinium enhancement by cardiac MRI: cardiac magnetic resonance imaging is emerging as a means of identifying patients who are at increased risk for arrhythmias. Several studies have found the presence of myocardial fibrosis by late gadolinium enhancement to be associated with the occurrence of ventricular arrhythmias.[33] [34] [35] [36] [37] The presence of fibrosis has also been found to be an independent risk for death.[32]

Investigation for ischaemia

Ischaemia may be related to myocardial bridging, LVOTO, or massive hypertrophy with reduced myocardial perfusion. The presence of ischaemia is a weak risk factor for SCD. Patients with angina or ST depression on exercise ECG should be evaluated for ischaemia with nuclear imaging or CT arteriography if the likelihood of coronary artery disease (CAD) is relatively low. CT arteriography or cardiac catheterisation are indicated if there is a higher likelihood of CAD given other patient factors.[2] [41] Myocardial bridging (tunnelling of coronary arteries into the heart muscle) should also be considered in the setting of angina or ischaemia. Cardiac catheterisation or CT arteriography can be used to evaluate bridging with specific attention given by the interpreter to this possible diagnosis.[42]

Genetic mutation analysis

Genetic testing in an individual with cardiomyopathy (known as confirmatory testing or diagnostic testing) is recommended for their direct benefit: (i) to confirm the diagnosis; (ii) where it may inform prognosis; (iii) where it may inform treatment selection; or (iv) where it may inform their reproductive management. Genetic testing of an affected individual may also be indicated if there are relatives who may benefit from testing, particularly those who will be enrolled in long-term surveillance if the genetic aetiology is not established (and who may be spared this burden if a genetic diagnosis is made in the family).[1]

The clinical utility of genetic testing has limitations. Currently identified disease-causing genes are thought to account for only 80% of cases. Moreover, the sensitivity of commercially available genetic testing depends on the number of genes screened for by the particular laboratory and may be <80%. When the 8 most common sarcomeric mutations are screened, the clinical sensitivity approaches 60%.[17] In up to 40% of patients with HCM, no sarcomere variant is identified, and there is no family history of disease.[43] The absence of a monogenic disease-causing variant on conventional genetic testing leaves three possibilities: (i) either there is a monogenic cause that has not been identified (i.e., not detected or recognised as causative by current testing); (ii) the cardiomyopathy does not have a genetic aetiology; or (iii) the cardiomyopathy is attributable to the effects of multiple variants of individually smaller effect.[1]

Despite its limitations, genetic testing is of value in screening family members of an affected patient with an identified mutation. Genetic testing in this situation will determine who requires ongoing clinical evaluation (known as cascade testing):[1] [2] [43][44]

- Relatives with the identified mutation should continue to be screened for the clinical development of HCM. The development of clinically apparent disease may occur late in adulthood, so screening should be lifelong.

- Gene-negative relatives can be reassured that they do not have the disease-causing mutation and do not require further screening.

While identification of a gene mutation during cascade testing indicates that the development of HCM is very likely, genotype-phenotype variability exists. Despite identical gene mutations, the gene mutation may manifest as HCM, restrictive cardiomyopathy, dilated cardiomyopathy, or no clinically apparent abnormality in different patients. For those without apparent disease, late-onset penetrance must be considered.[45] The risk of sudden death may be low or high for the same mutation.[46]

Genetic counselling should be available for all patients who are offered genetic testing, to inform decision-making and ensure that results can be reviewed and their clinical significance appropriately determined.[1] The importance of potential psychological, social, legal, ethical, and professional implications of having a genetic disease should also be discussed, and appropriate support provided.[2] Antenatal genetic counselling should be offered to parents who have had a previous affected child with an inherited HCM due to a single or multiple pathogenic variant(s), or to couples where one or both partners carries a known pathogenic variant.[1] [47] The risk of disease transmission should be discussed, as well as potential reproductive options (e.g., in-vitro fertilisation with preimplantation genetic diagnosis, antenatal genetic screening, and postnatal genetic testing).[2] [43]

Advances in genetic sequencing technology and increased accessibility to testing have led to an increasing number of incidentally identified genetic variants associated with HCM. Interpreting the clinical relevance of such findings can be challenging; the American Heart Association has produced guidance on how to manage them, with emphasis on a multi-disciplinary team approach.[48] The American College of Medical Genetics and Genomics has recommended that cardiomyopathy-associated genes be evaluated for secondary findings whenever broad clinical sequencing is undertaken, regardless of the initial indication for testing.[49] There is currently no international consensus around this recommendation, however.[1]

DIAGNOSIS

History and exam

Key diagnostic factors

family history of HCM (common)

- Autosomal dominant pattern but variable penetrance.

history of pre-syncope or syncope (common)

- Syncope with exertion or without a prodrome is particularly concerning and may be due to either outflow tract obstruction or a ventricular arrhythmia.

systolic ejection murmur (common)

- Audible at the lower left edge, accentuated by exercise and standing and lessened by lying supine or squatting.[4]

left ventricular lift (heave) (common)

- Best palpated at the left ventricular apex

double apical impulse or double carotid pulsation (common)

- An initial upstroke of the apical impulse or pulse may be felt, followed by a brief collapse and a second impulse. This transient interruption in cardiac output occurs when the anterior leaflet of the mitral valve is pulled into the left ventricular outflow tract during systole (systolic anterior motion of the mitral valve).

family history of sudden death (uncommon)

- Affected family members may have presented with sudden death, thereby eluding a definitive diagnosis.[4]

Other diagnostic factors

younger male (<50 years) (common)

- Males are typically diagnosed at a younger age (<50 years) and are often asymptomatic at time of diagnosis (detected on routine clinical evaluation).
- HCM is most commonly diagnosed in patients aged 30 to 50 years.[10] [12]

dyspnoea (common)

- Some patients may experience dyspnoea.[1][4]
- Dyspnoea on exertion may be due to left ventricular outflow tract obstruction, diastolic dysfunction, or end-stage heart failure related to HCM.

angina (common)

- Some patients may experience angina.[1]
- Chest pain with exertion is particularly concerning and may be due to massive hypertrophy with impaired coronary perfusion, outflow tract obstruction, or myocardial bridging (tunnelling of coronary arteries into heart muscle). Atherosclerotic coronary artery disease should also be considered in the adult with exertional chest pain.

palpitations (common)

- May represent either ventricular arrhythmias or atrial fibrillation.

irregularly irregular pulse (common)

- A sign of atrial fibrillation.
- Atrial fibrillation predisposes to thrombus formation and warrants anticoagulation as well as anti-arrhythmic therapies.

older female (>50 years) (uncommon)

- Females are much more likely to be diagnosed at a later age and be symptomatic at the time of diagnosis.[12]

collapse (uncommon)

- Patients may present with resuscitated sudden death or syncope with extreme exertion. This may be the only symptom.[4] [29]

fourth heart sound (uncommon)

- A fourth heart sound (S4) occurs late in diastole and suggests a stiff ventricle or impaired diastolic filling related to hypertrophy.
-

Risk factors

Strong

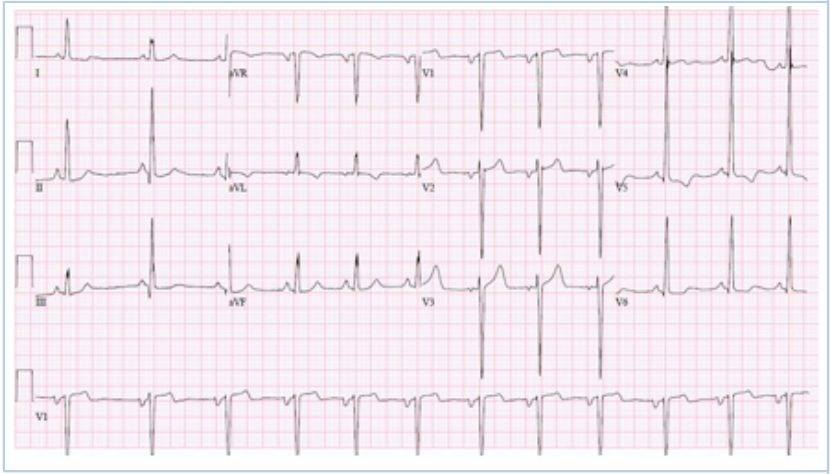
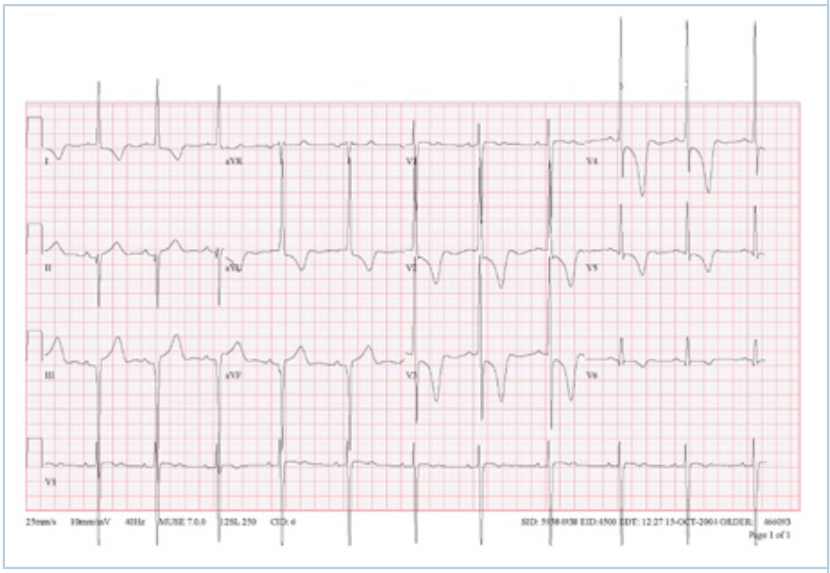
family history of HCM or sudden cardiac death

- Affected family members may have presented with sudden death, thereby eluding a definitive diagnosis.[4]
- There may be a family history of ventricular fibrillation or sustained ventricular tachycardia; unexplained syncope; non-sustained ventricular tachycardia, defined as 3 or more beats at ≥120 bpm on ambulatory (Holter) ECG; or maximum left ventricular wall thickness ≥30 mm.[2]

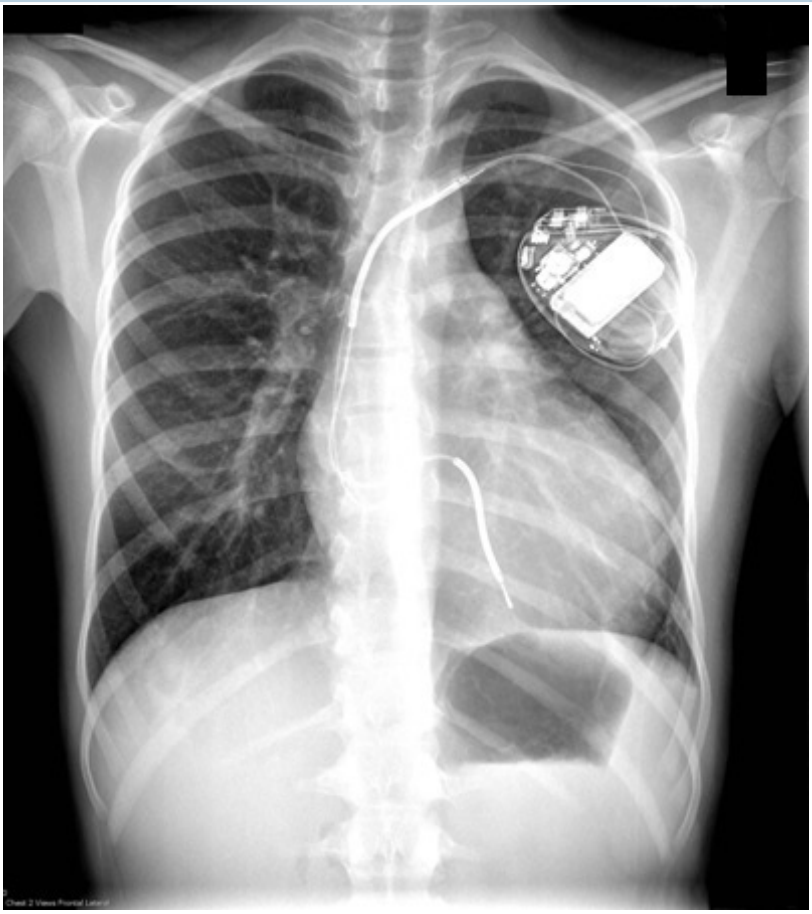
Investigations

1st test to order

Test	Result
ECG • A resting 12-lead ECG is recommended at the first clinic visit in all individuals with known or suspected hypertrophic cardiomyopathy (HCM) and should be repeated whenever there is a change in symptoms in patients with an established diagnosis.[1] Most patients have ECG abnormalities; these are not specific to HCM, but rather, should prompt further investigation with echocardiography. An abnormal ECG may predate the finding of hypertrophy on echocardiography.[23] • Repolarisation abnormalities are common. T-wave inversion commonly involves the inferior and lateral leads and T waves are deep and often preceded by ST-segment depression.[24] Deeply inverted T waves in the precordial leads are suggestive of apical HCM.[25] • Prominent abnormal Q waves may be seen in the inferior (II, III, aVF) and/or lateral (I, aVL, V5-6) leads, reflecting septal hypertrophy.[25] • Increased QRS voltages indicating left ventricular hypertrophy (LVH) may be present. These are nearly always associated with other ECG abnormalities in HCM.[24] The presence of isolated QRS voltage criteria for LVH in the absence of other ECG markers is present in fewer than 2% of patients with HCM.[26] • ECG signs of left and right atrial enlargement and P-wave prolongation (a known predictor of atrial fibrillation) may be observed. They rarely occur in isolation; other ECG abnormalities such as repolarisation changes or signs of LVH are generally present. Left atrial enlargement reflects diastolic dysfunction, high filling pressures, outflow obstruction, and functional mitral regurgitation. Left atrial dilatation and dysfunction are markers of adverse prognosis.[24] • Left-axis deviation (caused by LVH) and ventricular pre-excitation may also be seen.[24] • Some patients may present with arrhythmias; for example, atrial fibrillation or supraventricular tachycardia.[24] • The ECG is normal in only a small proportion (5% to 10%) of patients at presentation.[1] [25] These patients have been reported	**ST-T wave abnormalities; prominent Q waves; LVH; P-wave abnormalities; left-axis deviation; ventricular pre-excitation; may be normal**

Test	Result
to have a more favourable clinical course than those with ECG abnormalities.[26] •  *ECG showing changes associated with LVH* *From the collection of Melanie Everitt MD, Heart Failure & Transplantation Program, Primary Children's Medical Center, Salt Lake City, UT; used with permission*  *Giant T-wave inversion* *From the collection of Dr Anji T. Yetman MD, University of Utah*	
creatine kinase (CK) • US guidelines do not recommend laboratory tests as part of the initial work-up.[2] However, European guidelines recommend that all patients with suspected or confirmed hypertrophic cardiomyopathy (HCM) should have routine laboratory tests done to establish aetiology, assess disease severity, and aid in the detection of extracardiac manifestations and assessment of secondary organ dysfunction.[1] • Raised CK levels are a useful clue when trying to establish aetiology; metabolic disorders such as Danon or mitochondrial disease, which can mimic HCM, should be considered.[50] When CK is persistently raised, a detailed examination by a neurologist should be considered.[1]	**normal; raised levels should raise suspicion of metabolic disorders**

Test	Result
liver function tests • US guidelines do not recommend laboratory tests as part of the initial work-up.[2] However, European guidelines recommend that all patients with suspected or confirmed hypertrophic cardiomyopathy (HCM) should have routine laboratory tests done to establish aetiology, assess disease severity, and aid in the detection of extracardiac manifestations and assessment of secondary organ dysfunction.[1] • Liver dysfunction is prevalent in patients with chronic heart failure.[51] Abnormal liver function tests can also be a useful clue when trying to establish aetiology; metabolic disorders such as Danon's disease, which can mimic HCM, should be considered.[50]	**normal; may be abnormal in patients with chronic heart failure**
renal function tests • US guidelines do not recommend laboratory tests as part of the initial work-up.[2] However, European guidelines recommend that all patients with suspected or confirmed hypertrophic cardiomyopathy should have routine laboratory tests done to establish aetiology, assess disease severity, and aid in the detection of extracardiac manifestations and assessment of secondary organ dysfunction.[1] • Impaired renal function may be seen with severe left ventricular dysfunction.[52]	**may be abnormal in patients with severe left ventricular dysfunction; normal**
N-terminal pro-brain natriuretic peptide (NT-proBNP) • US guidelines do not recommend laboratory tests as part of the initial work-up.[2] However, European guidelines recommend that all patients with suspected or confirmed hypertrophic cardiomyopathy should have routine laboratory tests done to establish aetiology, assess disease severity, and aid in the detection of extracardiac manifestations and assessment of secondary organ dysfunction.[1] • High NT-proBNP levels are associated with cardiovascular events, heart failure, and death, and may have diagnostic, prognostic, and therapeutic monitoring value.[1]	**raised in heart failure; may be normal**
troponin • US guidelines do not recommend laboratory tests as part of the initial work-up.[2] However, European guidelines recommend that all patients with suspected or confirmed hypertrophic cardiomyopathy should have routine laboratory tests done to establish aetiology, assess disease severity, and aid in the detection of extracardiac manifestations and assessment of secondary organ dysfunction.[1] • Raised troponin levels are associated with a higher risk of cardiovascular events, heart failure, and death, and may have diagnostic, prognostic, and therapeutic monitoring value.	**raised levels indicate increased risk of cardiovascular events; may be normal**
urinalysis • US guidelines do not recommend laboratory tests as part of the initial work-up.[2] However, European guidelines recommend that all patients with suspected or confirmed hypertrophic cardiomyopathy should have their urine checked for protein; proteinuria is suggestive of renal impairment.[1]	**proteinuria; normal**
CXR • This test is not particularly sensitive. Patients may have cardiomegaly secondary to left ventricular hypertrophy or left atrial enlargement, or the CXR may be normal.[4]	**cardiomegaly; normal**

Test	Result
 *CXR of a patient with HCM demonstrating cardiomegaly* *From the collection of Melanie Everitt MD, Heart Failure & Transplantation Program, Primary Children's Medical Center, Salt Lake City, UT; used with permission*	
transthoracic echocardiography with Doppler • At initial assessment of all patients with hypertrophic cardiomyopathy (HCM), transthoracic 2D and Doppler echocardiography are recommended. The classic finding is left ventricular hypertrophy (LVH), typically asymmetric hypertrophy of the septum.[4] [27] • Echocardiography is also used for family screening of an affected individual, and for risk assessment of sudden cardiac death (SCD) in patients with a known diagnosis of HCM. • Clinical diagnosis of HCM is confirmed when maximal end-diastolic wall thickness ≥15 mm is imaged anywhere in the left ventricle (LV). More limited hypertrophy (≥13 mm) can be diagnostic when present in family members of a patient with HCM or in conjunction with a positive genetic test.[2] [27] • Systolic anterior motion of the mitral valve may also be seen, along with mitral insufficiency. • LV outflow tract obstruction (LVOTO) may be present.[2] By convention, LVOTO is defined as a peak instantaneous Doppler LV outflow tract gradient of ≥30 mmHg, but the threshold for invasive treatment is usually considered to be ≥50 mmHg.[1] • There may also be abnormalities of diastolic function (present in 80% of patients independent of the presence of LVOTO).[2] Diastolic dysfunction should be assessed by Doppler tissue imaging as part	**LVH, typically asymmetric septal hypertrophy; left ventricular outflow tract obstruction may or may not be present; diastolic dysfunction may or may not be present**

Test	Result
of the echocardiographical screening test of first-degree relatives, as this abnormality may precede the onset of overt LVH.[27] [28]	

Other tests to consider

Test	Result
exercise ECG • Exercise testing is performed to aid in risk stratification. • Abnormalities associated with an increased risk of sudden death include: abnormal blunted systolic BP response of <20 mmHg to exercise, ventricular arrhythmias, progressive ST depression, and symptoms.[29] [30]	**may be normal or may demonstrate reduction in maximal oxygen consumption, abnormal blunted BP response, ST segment depression, arrhythmias**
Holter monitoring • Ventricular arrhythmias are associated with an increased risk of sudden death.	**may be normal or demonstrate ventricular or supraventricular arrhythmias**
nuclear imaging exercise test • Patients with exertional chest pain or ventricular tachycardia on Holter monitoring should undergo nuclear testing with either single-photon-emission computed tomography or positron emission tomography.[27] Myocardial perfusion imaging may demonstrate perfusion defects even in the absence of obstructive lesions.[2] Patients may have fixed or reversible defects. Patients with reversible defects should undergo cardiac catheterisation to identify possible causes of ischaemia. • Nuclear medicine can also play a role in diagnosis; it is particularly helpful in the aetiological diagnosis of cardiac amyloidosis.[1]	**may be evidence of ischaemia**
cardiac magnetic resonance (CMR) • Contrast-enhanced CMR can be a useful adjunct in patients with hypertrophic cardiomyopathy (HCM) at initial evaluation.[1] [2] It can aid diagnosis and contribute to risk stratification and management. Left ventricular (LV) wall thickness can be assessed; the use of CMR may thus increase the diagnostic yield in patients with suspected HCM who have poor visualisation by echocardiogram of the LV walls or LV apex.[1] [2] [27] • Systolic and diastolic function can also be assessed, as well as mitral valve function, LV outflow tract obstruction, and left atrial dimensions.[1] • The use of late gadolinium enhancement techniques can identify areas of myocardial fibrosis that may be a marker for adverse outcomes, or may aid in differentiating HCM from an athletic heart.[31] • CMR is also emerging as a means of identifying patients who are at increased risk for arrhythmias. Several studies have found the presence of myocardial fibrosis by late gadolinium enhancement to be associated with the occurrence of ventricular arrhythmias, as well as an independent risk factor for death.[2] [32] [33] [34] [35] [36] [37] • Tissue characterisation on CMR can provide clues regarding aetiology, as characteristic findings are associated with certain diseases, for example, in sarcomeric HCM, a patchy mid-wall in hypertrophied areas is typical, while in amyloidosis-related cardiac hypertrophy, diffuse subendocardial late gadolinium enhancement is seen. These findings should be assessed collectively with genetic	**LVH; may show left ventricular outflow tract obstruction, structural abnormalities of mitral valve and papillary muscle, systolic and/or diastolic dysfunction, and left atrial enlargement; later in disease course: may demonstrate myocardial fibrosis**

Test	Result
results and other clinical features by operators expert in cardiac imaging and the evaluation of heart muscle disease.[1] • Serial follow-up CMR, every 2-5 years depending on initial severity and clinical course, can assist in evaluating disease progression as well as the benefits of therapy.[1]	
cardiac computed tomography (CT) • Although not used commonly, CT can provide important insights when echocardiography is technically limited and imaging is contraindicated or unavailable.[2] Cardiac CT provides clear definition of left ventricular structure (including hypertrophy pattern, wall thickness measurement, detection of subaortic membrane, and intracardiac thrombus) and function. Disadvantages of CT are the use of radiation and radioiodine contrast and inferior temporal resolution compared with echocardiography.[2]	**LVH; may show systolic anterior motion of mitral valve, intracardiac thrombi and patchy or diffuse delayed iodine enhancement**
CT coronary arteriography • Indicated in patients with exertional chest pain or ischaemia on nuclear testing to check for the presence of concomitant atherosclerotic coronary disease or myocardial bridging.[1] [2] [27]	**usually normal; may be evidence of atherosclerotic coronary artery disease**
cardiac catheterisation • In symptomatic patients with hypertrophic cardiomyopathy and inconclusive non-invasive cardiac imaging, left and right heart catheterisation may be considered to assess the severity of left ventricular outflow tract obstruction and to measure LV filling pressures.[1] [2] • Patients with exertional chest pain, ischaemia on nuclear testing, or an increased probability of coronary artery disease based on risk factors should undergo cardiac catheterisation to rule out co-existent atherosclerotic coronary disease or myocardial bridging.[2] Also recommended for patients who are candidates for septal reduction therapy.[2]	**usually normal; may be evidence of atherosclerotic coronary artery disease**
stress echocardiography • Can be helpful in selected patients to evaluate myocardial ischaemia.[1]	**normal; myocardial ischaemia**
exercise echocardiography • Can be useful to identify provocable left ventricular outflow tract obstruction and exercise-induced mitral regurgitation in symptomatic patients with hypertrophic cardiomyopathy.[1]	**normal; myocardial ischaemia**
trans-oesophageal echocardiography • Limited to select indications, such as the exclusion of atrial thrombi related to atrial fibrillation, investigating the method of obstruction in patients with left ventricular outflow tract obstruction where this is not obvious, elucidating the mechanism of mitral regurgitation, or planning invasive interventions such as septal myectomy.[1]	**LVH; may show other abnormalities such as atrial thrombi or intrinsic mitral valve abnormality**
endomyocardial biopsy • Not usually recommended for diagnosis of hypertrophic cardiomyopathy but may be considered on rare occasions, especially when the pattern of hypertrophy is diffuse and there is suspicion for other cardiomyopathies presenting with hypertrophy.[1]	**may show features of alternative cause for LV hypertrophy, such as storage disease (e.g., Fabry disease) or infiltrative process (e.g., amyloidosis)**

Test	Result
genetic mutation analysis • Currently identified disease-causing genes are thought to account for 80% of cases of the disease, and the sensitivity of commercially available genetic testing may be lower depending on the number of genes screened for by the particular laboratory. When the eight most common sarcomeric mutations are screened for, the clinical sensitivity approaches 60%.[17] In up to 40% of patients with hypertrophic cardiomyopathy (HCM), no sarcomere variant is identified, and there is no family history of disease.[43] The absence of a monogenic disease-causing variant on conventional genetic testing leaves three possibilities: (i) either there is a monogenic cause that has not been identified (i.e., not detected or recognised as causative by current testing); (ii) the cardiomyopathy does not have a genetic aetiology; or (iii) the cardiomyopathy is attributable to the effects of multiple variants of individually smaller effect.[1] • When a mutation is identified, genetic testing is useful for screening other relatives to determine requirement for ongoing cardiology follow-up. Relatives with the identified mutation should continue to be screened for the clinical development of HCM. The development of clinically apparent disease may occur late in adulthood, so screening should be lifelong. Gene-negative relatives can be reassured that they do not have the disease-causing mutation and do not require further screening.[1] [2] [43][44] • Clinical variability exists despite identical gene mutations. The risk of sudden death may be low or high for the same mutation.[46] • Genetic counselling should be available for all patients who are offered genetic testing, to inform decision-making and ensure that results can be reviewed and their clinical significance appropriately determined.[1] The importance of potential psychologic, social, legal, ethical, and professional implications of having a genetic disease should also be discussed, and appropriate support provided.[2] • Antenatal genetic counselling should be offered to parents who have had a previous affected child with an inherited HCM due to a single or multiple pathogenic variant(s), or to couples where one or both partners carries a known pathogenic variant.[1] [47] The risk of disease transmission should be discussed, as well as potential reproductive options (e.g., in-vitro fertilisation with preimplantation genetic diagnosis, antenatal genetic screening, and postnatal genetic testing).[2] [43] • Advances in genetic sequencing technology and increased accessibility to testing have led to an increasing number of incidentally identified genetic variants associated with HCM. Interpreting the clinical relevance of such findings can be challenging; the American Heart Association has produced guidance on how to manage them, with emphasis on a multi-disciplinary team approach.[48] The American College of Medical Genetics and Genomics has recommended that cardiomyopathy-associated genes be evaluated for secondary findings whenever broad clinical sequencing is undertaken, regardless of the initial indication for testing.[49] There is currently no international consensus around this recommendation, however.[1]	**mutation in 1 of the identified genes**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Athlete's heart	• Patient will typically be a male endurance athlete without cardiac symptoms. • No family history of HCM or sudden death. • Hypertrophy will regress with cessation of exercise.[53]	• Echocardiography: will characteristically show increased left ventricular (LV) chamber dimension (LV end-diastolic dimension or LV end-diastolic >55 mm), symmetrical left ventricular hypertrophy (LVH) with a homogeneous-appearing myocardium. • Wall thicknesses may occasionally exceed upper normal limits (12 mm).[53] • LV filling pattern is most often normal.[53] • The use of late gadolinium enhancement techniques may aid in differentiating HCM from an athletic heart.[31]
Discrete subaortic stenosis	• No family history of HCM or sudden death. • Not associated with sudden death. Systolic murmur is typically present in all positions (i.e., supine and squatting).	• Echocardiography: symmetrical left ventricular hypertrophy; aortic valve closure early in systole and persistent valve closure throughout the rest of systole; coarse fluttering of the aortic valve leaflets.[54]
LVH due to hypertension	• History of long-standing hypertension.	• Echocardiography: most commonly concentric left ventricular hypertrophy or remodelling with varying degrees of diastolic dysfunction depending on the severity and duration of hypertension.[27]

Criteria

2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy[2]

- Left ventricular hypertrophy (LVH) associated with non-dilated ventricular chambers in the absence of another cardiac or systemic disease that itself would be capable of producing the magnitude of hypertrophy evident.
- In adults, hypertrophic cardiomyopathy (HCM) is usually recognised by maximal left ventricular (LV) wall thickness 15 mm or greater, with wall thickness of 13 to 14 mm considered borderline,

particularly in the presence of other compelling information (e.g., family history of HCM), based on echocardiography.

- Any degree of wall thickness is compatible with the presence of the HCM genetic substrate, and family members may also have disease-causing sarcomere mutations but no evidence of LVH.

2023 ESC guidelines for the management of cardiomyopathies[1]

- LVH that is not solely explained by abnormal loading conditions.
- In adults, HCM is defined by a wall thickness of 15 mm or greater in any myocardial segment. Wall thickness of 13 to 14 mm requires evaluation of other features, including family history, genetic findings, ECG abnormalities, and echocardiography.
- In first-degree relatives of patients with unequivocal disease (LVH ≥15 mm), diagnosis is based on wall thickness ≥13 mm in any myocardial segment.

The Cardiac Society of Australia and New Zealand position statement for the diagnosis and management of hypertrophic cardiomyopathy[55]

- LVH, typically asymmetrical in distribution, in the absence of another cardiac cause or systemic condition capable of producing the magnitude of hypertrophy, such as hypertension.
- HCM is usually recognised by a maximal left ventricular wall thickness of 15 mm or greater in adults; 13 to 14 mm is considered borderline, unless there is a definite family history of HCM. Mild hypertrophy related to intense athletic conditioning may occur but should normalise after a period of deconditioning.
- Myocardial biopsy is not needed for the diagnosis but shows characteristic features of myocyte hypertrophy, fibre disarray, and interstitial fibrosis.

Screening

Screening should be performed in two distinct populations:

- Competitive athletes
- Family members of affected patients.

Screening of competitive athletes

- Screening of competitive athletes for hypertrophic cardiomyopathy (HCM) remains a controversial topic.[56] [57] [58] The argument has been made that routine screening should be performed in all competitive athletes, as HCM is the most common cause of sudden death in this population.[56]
- While only a minority of athletes will have significant repolarisation abnormalities suggestive of a congenital cardiomyopathy or inherited channelopathy, pre-participation screening with ECG has been routinely performed on all competitive athletes in Italy since 1982. Based on this experience, it has been suggested that the low incidence of sport-related sudden death in Italy has occurred as a result of such screening.[58]
- While ECG increases the sensitivity of detecting underlying heart disease above physical examination alone, a normal ECG may be present in up to 25% of asymptomatic patients with HCM.[59]

- Although in Europe the use of ECG screening in young athletes has been associated with a decline in the rate of sudden cardiac death (SCD) in this population, this approach has not been endorsed in the US.[59]
- Internationally agreed criteria have been published to help non-experts interpret the ECG in athletes.[60] This consensus statement defines the ECG findings that warrant further evaluation for disorders that predispose to SCD.
- The significance of T-wave inversions in asymptomatic athletes is largely dependent on age, sex, ethnicity, and duration and intensity of athletic training. It is important to quantify SCD risk in the context of other relevant findings, such as family history of SCD and other findings of underlying structural disease. It is generally accepted that anterior T-wave inversions are a normal variant in black people and adolescents. In contrast, T-wave inversions seen in the lateral leads in any patient are usually abnormal, and suggestive of underlying cardiac disease.[61]

Screening of family members

- Routine screening of all first-degree family members should be performed by echocardiography. As the hypertrophy may not develop until a later age, a negative echocardiogram importantly does not rule out the diagnosis.[15] [45]
- Guidelines from the American Heart Association/American College of Cardiology recommend that initial screening in children and adolescents from genotype-positive families and families with early-onset disease should happen at the time HCM is diagnosed in a first-degree family member.[2] For all other children and adolescents, initial screening is recommended any time after HCM is diagnosed in a family member, but no later than puberty. Initial screening for adults is also recommended at the time HCM is diagnosed in a first-degree family member.[2]
- Clinical screening with history, physical examination, ECG, and echocardiogram should be repeated every 12 to 24 months throughout adolescence.
- Due to the possibility of delayed adult-onset left ventricular hypertrophy, family members older than 18 years should continue to undergo clinical screening every 3 to 5 years.[2] [62]
- Echocardiograms should not be performed more frequently than 12 months as there is unlikely to have been interval change within that time period.
- Genetic analysis is an important screening tool for extended family members when a genetic mutation has been identified within affected family members. Genetic screening of relatives can then be used to definitively rule out the diagnosis in unaffected individuals, thereby avoiding the need for lifelong serial echocardiographical screening.[15] [46]

Approach

There is no curative treatment for hypertrophic cardiomyopathy (HCM). Therapies are advocated in select patient populations in order to reduce symptoms (which may occur secondary to subaortic obstruction, diastolic dysfunction, or ischaemia) and to reduce the risk of sudden cardiac death (SCD). Patient care requires the collaboration of different specialties and coordination between different levels of care; a shared care approach between cardiomyopathy specialists and general adult cardiology centres is strongly recommended.[1]

Initial assessment and approach to treatment in all patients

On initial evaluation, patients must be classified as asymptomatic or symptomatic. They must also undergo risk stratification to further define their risk of SCD.[1] [2] Only patients with symptoms related to outflow tract obstruction, diastolic dysfunction, or systolic dysfunction require medical therapy. Only certain patients at high risk for SCD warrant implantable cardioverter-defibrillator (ICD) placement.

Arrhythmic risk calculators may be useful in predicting the risk of SCD and have been validated in large populations.[63] [64] One study, however, evaluated the 2014 European Society of Cardiology SCD risk model for HCM. The prognostic score was applied retrospectively to a large independent cohort of patients with HCM and was found to be generally unreliable for prediction of future SCD; most patients who had experienced SCD or undergone appropriate ICD interventions were misclassified as low risk.[39]

Consensus recommendations have previously restricted all athletes with HCM from all competitive sports; however, US and European guidelines now advise that participation in high-intensity exercise/competitive sports may be considered for some individuals after comprehensive evaluation and shared discussion.[2] [65] A large prospective cohort study found that among individuals with HCM, or those who are genotype positive/phenotype negative, who are treated in experienced centres, those exercising vigorously do not experience a higher rate of death or life-threatening arrhythmias than those exercising moderately or those who are sedentary.[66]

Patients at high risk of sudden death

SCD is the most common mode of death in young people with HCM, occurring with an incidence of 1% per year.[67] The proposed mechanism of SCD is ventricular tachycardia (VT) or ventricular fibrillation (VF) secondary to ischaemia.[4] SCD typically occurs in the setting of extreme exertion. No medical or surgical treatment has been shown to lessen the risk of sudden death in large populations, thus ICD therapy is first-line therapy in those patients in whom the risk of SCD is considered significant.[2] For details of risk stratification, see Diagnostic approach .

Guidelines recommend ICD placement for patients with HCM and previous documented cardiac arrest or sustained ventricular arrhythmia causing syncope or haemodynamic compromise in the absence of reversible causes.[1] [2] Routine diagnostic testing to evaluate the risk of SCD is recommended, regardless of symptom status.[2] European guidelines recommend comprehensive SCD risk stratification in all patients at initial presentation, then at 1-2 year intervals or whenever there is a change in clinical status.[1]

No randomised controlled trials (RCTs) studying the effect of ICD placement have been performed in patients with HCM, although there is evidence from observational studies.[2] [68]

A single marker of high risk for sudden cardiac arrest may be sufficient to consider prophylactic ICD placement in selected patients.[1] [2][68] Patients in whom this would apply include those with one or more first-degree or close relatives 50 years of age or less with sudden death presumably caused by HCM, patients with a maximum LV wall thickness greater than or equal to 30 mm, patients with one or more recent episodes of syncope suspected to be arrhythmic, LV apical aneurysm, LV systolic dysfunction with ejection fraction <50%, and late gadolinium enhancement >15% on cardiac magnetic resonance imaging.[1] [2]

Complications following ICD placement have been reported to occur at a rate of 3.4% per year.[69] Contact sports should be avoided after ICD implant.[70]

Patients and carers should be fully informed and participate in decision-making regarding ICD placement.[2] They should be counselled on the risk of inappropriate shocks, implant complications, and the social, occupational, and driving implications of the device. Implantation of a cardioverter defibrillator is only recommended in patients who have an expectation of good-quality survival >1 year.[1]

Asymptomatic patients: not at high risk of sudden death

If the patient is not considered at high risk of SCD, ICD placement is not required. Patients in this category who are asymptomatic should be closely observed for the development of HCM. US and European guidelines now advise that for those who are genotype-positive and phenotype-negative (asymptomatic without evidence of left ventricular hypertrophy [LVH] on cardiac imaging), participation in competitive sport of any intensity is reasonable.[2] [65] These patients should be regularly assessed for change in clinical status.

Symptomatic patients: predominantly left ventricular outflow tract obstruction (LVOTO) with preserved systolic function

In symptomatic patients with LVOTO, the aim is to improve symptoms by using drugs, surgery, or alcohol septal ablation. A symptomatic patient with resting or provocable LVOTO is initially treated with negative inotropic or chronotropic therapy. Tachyphylaxis to medication is common, and medication dosage must be adjusted over time. In the absence of many RCTs, pharmacological therapy is mostly administered on an empirical basis to improve functional capacity and reduce symptoms.[1]

Beta-blockers

- Beta-blockers are beneficial due to their negative inotropic and chronotropic properties. Non-vasodilating beta-blockers are considered first-line therapy for symptomatic HCM due to LVOTO. In standard doses, they are usually well tolerated. Reported side effects include fatigue, impotence, sleep disturbances, and bradycardia.
- Substantial experience suggests that beta-blockers can mitigate symptoms and reduce outflow tract obstruction in those patients with LVOTO occurring with exercise. There is little evidence to suggest a beneficial effect on resting outflow tract gradients; however, one small RCT found that metoprolol reduced LVOTO at rest and during exercise, provided symptom relief, and improved quality of life in patients with obstructive HCM. Maximum exercise capacity remained unchanged. This is the first RCT in over 50 years to address the use of beta-blockers in HCM.[71] [72]
- Beta-blocker may be of benefit in patients with HCM and symptoms suggestive of ischaemia.

Non-dihydropyridine calcium-channel blockers

- Used for relief of symptoms, including those with a component of chest pain.[2] Verapamil and diltiazem have vasodilating properties as well as negative inotropic and chronotropic effects.[2] Short-term oral administration may increase exercise capacity, improve symptoms, and normalise or improve LV diastolic filling without altering systolic function.[1]
- Verapamil can be used when beta-blockers are contraindicated or ineffective, but it is potentially harmful in patients with obstructive HCM and severe dyspnoea at rest, hypotension, and very high resting gradients (e.g., >100 mmHg), and infants <6 weeks of age.[2] Verapamil has been reported to cause death in a few HCM patients with severe LVOTO or elevated pulmonary arterial pressure as it may provoke pulmonary oedema.[1] It should therefore be used with caution in these patients.[2] As a result, some favour disopyramide as second-line therapy over calcium-channel blockers.[4]
- Diltiazem should be considered in patients who are intolerant or have contraindications to beta-blockers and verapamil.[1]

Disopyramide

- Negative inotrope and a type IA anti-arrhythmic agent. For patients with LVOTO and persistent severe symptoms despite therapy with beta-blockers or non-dihydropyridine calcium-channel blockers, adding disopyramide is recommended.[1] [2]
- Often disopyramide is used in combination with an agent that has atrioventricular nodal blocking properties as it may increase the ventricular rate in patients with atrial fibrillation.
- It may be considered as monotherapy in patients who are intolerant of or have contraindications to beta-blockers and calcium-channel blockers.[1]
- Disopyramide decreases resting LVOTO. In one multicentre study it was shown that 75% of patients with obstructive HCM who were managed with disopyramide had amelioration of symptoms in association with a 50% reduction in LV outflow gradient. This beneficial effect was sustained for the study period of 3 years.[73]
- Dose-limiting anticholinergic side effects include dry eyes and mouth, urinary hesitancy or retention, and constipation. The ECG QT interval should be monitored for prolongation.[1]

Mavacamten

- A myosin inhibitor approved for the treatment of adults with symptomatic New York Heart Association (NYHA) class II-III obstructive HCM to improve functional capacity and symptoms.[1] [74] [75] It works by inhibiting cardiac myosin adenosine triphosphatase (ATPase), thus reducing actin-myosin cross-bridge formation; this reduces contractility and improves myocardial dynamics.[1]
- While mavacamten is approved for this indication in the US, the most recent guidelines from the American Heart Association and American College of Cardiology do not include a cardiac myosin inhibitor in the treatment cascade.[2] Mavacamten is currently available in the US through a Risk Evaluation and Mitigation Strategy (REMS) programme, designed to monitor patients periodically with echocardiograms for early detection of systolic dysfunction and to screen for drug interactions prior to each prescription.[76]
- European and UK guidelines now recommend mavacamten as a second-line treatment for patients with HCM and LVOTO.[1] [75] It should be considered when optimal medical therapy with beta-blockers, calcium-channel blockers, and/or disopyramide is ineffective or poorly tolerated. European guidelines stipulate that in the absence of evidence to the contrary, mavacamten should not be used with disopyramide, but may be coadministered with beta-blockers or calcium-channel

blockers.[1] UK guidelines differ, stating that it can be added-on to individually optimised standard care that includes beta-blockers, calcium-channel blockers, or disopyramide, unless these are contraindicated.[75]

- In patients with contraindications or known sensitivity to beta-blockers, calcium-channel blockers, and disopyramide, mavacamten may be considered as monotherapy.[1]
- Up-titration of medication to a maximum tolerated dose should be monitored in accordance with licensed recommendations using echocardiographic surveillance of LV ejection fraction.[1]
- In the EXPLORER-HCM phase 3 trial, treatment with mavacamten improved exercise capacity, LVOTO, NYHA functional class, and health status (symptoms, physical and social function, and quality of life) compared with placebo in patients with symptomatic obstructive HCM.[77] [78] [79] The drug was well tolerated and has a good safety profile; only a small subset of patients developed transient LV systolic dysfunction, which resolved after temporary discontinuation of the drug.
- A secondary analysis found favourable changes in cardiac structure and function through 30 weeks of therapy, including improvement in echocardiographic markers of LV filling pressures, LVOT gradients, and systolic anterior motion. Reductions in NT-proBNP were also seen, further supporting the benefit of mavacamten on functional improvement and favourable remodelling.[80]
- Interim data from a long-term extension study, analysed at a median follow-up of 62.3 weeks, showed that mavacamten was associated with clinically important and sustained improvements of LVOT gradients, NYHA class, and NT-proBNP levels that were consistent with those observed in the parent trial. Treatment was generally well tolerated over 315 patient-years of exposure.[76]
- In the VALOR-HCM phase 3 trial, patients who were assigned to mavacamten, as well as those who initially received placebo for 16 weeks and then crossed over to mavacamten, had a significantly reduced need for septal reduction therapy after 56 weeks compared with placebo.[81]
- In another randomised trial (EXPLORER-CN), Chinese patients with symptomatic obstructive HCM who received treatment with mavacamten had a significant reduction in Valsalva LV outflow tract peak gradient, compared with those treated with placebo[82]
- Open-label, follow-up studies evaluating the long-term efficacy and safety of mavacamten in these trials, as well as real-world experience, will provide more information on the durability of improvements and the safety profile of the drug.

Surgical myectomy (septal reduction therapy)

- If severe symptoms persist in the face of a resting or provocable outflow tract gradient of ≥50 mmHg, consideration should be given to surgical myectomy, which reduces septal mass, thereby relieving obstruction.[2] European guidelines specify that patients should be in New York Heart Association/Ross functional class III-IV, or be experiencing recurrent exertional syncope due to LVOTO, despite maximum tolerated medical therapy.[1]
- Myectomy abolishes or substantially reduces LV outflow tract gradients in over 90% of cases, reduces systolic anterior motion-related mitral regurgitation, and improves exercise capacity and symptoms.
- Long-term symptomatic benefit is achieved in >80% of patients, with a long-term survival comparable to that of the general population.
- Preoperative determinants of a good long-term outcome are: age <50 years; left atrial size <46 mm; absence of AF; and male sex.[1] Older age and increased severity of comorbidities are predictive of poor surgical outcomes.[83] Data from experienced centres suggest that institutions should aim for mortality rates of <1%.[2]
- Surgical myectomy has not been conclusively shown to affect the incidence of sudden death.

- The rate of postoperative complications is estimated at 5.9% in most experienced centres. The most common complications are complete heart block in patients without previous conduction abnormality (3% to 10%), left bundle branch block (40% to 56%), and ventricular septal defect (1%).[83] [84]

Alcohol septal ablation (ASA)

- May be performed as an alternative to surgical myectomy.
- Involves the delivery of alcohol into a target septal perforator branch of the left anterior descending coronary artery, for the purpose of producing a myocardial infarction and reducing septal thickness.[1]
- Septal remodelling and relief of obstruction after ASA occurs over several months, resulting in a smaller reduction in resting gradient compared with surgical myectomy, but a similar reduction in patient symptoms.[85] [86]
- Complications include ventricular arrhythmias (2.2%), coronary dissection (1.8%), and complete heart block (>10%) necessitating permanent pacemaker placement.[87] There is an increased need for permanent pacemaker implantation post-procedure compared with surgical myectomy.[88]
- Mortality from all-cause or sudden cardiac death is low after ASA.[89]
- ASA has not been conclusively shown to affect the incidence of sudden death.
- While data comparing the later outcomes of ASA and surgical myectomy are lacking, a retrospective, observational study compared long-term mortality of patients with obstructive HCM following both procedures. It concluded that ASA was associated with increased long-term all-cause mortality compared with septal myectomy. This finding remained after adjustment for confounding factors (patients undergoing ASA tend to be older with more comorbidities and reduced septal thickness, compared with patients undergoing septal myectomy), but may still be influenced by unmeasured confounders.[90]

Dual-chamber pacing

- May be an option in select patients with medically refractory symptomatic obstruction who are not candidates for, or who do not desire, surgery or ASA. Dual-chamber pacing is not a primary line of therapy; however, as efficacy is unproven in randomised, cross-over, blinded studies.[91] [92]
- Treatment is associated with subjective improvement in symptoms without objective improvement in exercise capacity.
- Gradient reduction is less than that achieved with surgery.[93]

Management of complications

Myocardial ischaemia

Patients may develop symptoms or signs of ischaemia. Ischaemia in HCM is multifactorial and thus not easily treated. Decreasing myocardial oxygen demand with negative inotropic and chronotropic agents may prove beneficial. Surgical unroofing of myocardial bridging (tunnelling of coronary arteries into heart muscle) has been reported to yield symptomatic improvement in select patients, but data are limited.[30] [94] Moreover, myocardial bridging is frequently identified in HCM and has not been conclusively linked to SCD.[95] [96] Therefore, the risks of the procedure need to be considered when advising surgical intervention.

Ventricular arrhythmias

Implantation of an ICD is recommended for secondary prevention in patients with HCM who have survived a cardiac arrest due to VT or VF, or who have spontaneous sustained ventricular arrhythmia causing syncope or haemodynamic compromise in the absence of reversible causes. It should also be considered in patients presenting with haemodynamically tolerated VT, in the absence of reversible causes.[1] In patients with HCM and pacing-capable ICDs, programming antitachycardia pacing is recommended to minimise risk of shocks.[2] Although data are lacking, anti-arrhythmic drugs such as beta-blockers (e.g., sotalol) and amiodarone should be considered for patients with recurrent, symptomatic ventricular arrhythmia, or recurrent ICD shocks.[1] Catheter ablation in specialised centres may be considered in select patients with recurrent, symptomatic sustained monomorphic VT (SMVT), or recurrent ICD shocks for SMVT, in whom anti-arrhythmic drugs are ineffective, contraindicated, or not tolerated.[2] [97]

Atrial arrhythmias

Atrial arrhythmias, including atrial fibrillation (AF), are common, particulary in older patients with HCM. Prevalence of AF among patients with HCM is estimated at 17% to 39%, with an annual incidence of 2.8% to 4.8%.[1] AF is often poorly tolerated in patients with HCM.[2] As a result, an aggressive strategy for maintaining sinus rhythm is warranted. Paroxysmal or chronic AF are linked to left atrial enlargement.[4] AF is independently associated with heart-failure-related death, and occurrence of fatal and non-fatal stroke, as well as long-term progression of heart failure symptoms.[2] Management of AF is as per patients without HCM. However, digoxin is not typically used for atrial rate control if the patient has significant hypertrophy, as there is a theoretical concern that it could exacerbate LVOTO due to a positive inotropic effect.[2] In addition, traditional stroke risk scoring systems used in the general population, such as CHA2DS2-VASc (congestive heart failure or left ventricular dysfunction, hypertension, age ≥75 [doubled], diabetes, stroke [doubled]-vascular disease, aged 65-74 years, sex category [female]) are not predictive in patients with HCM, with evidence suggesting that they may perform suboptimally.[1] [2] [98] For this reason, although there are no RCTs evaluating the role of anticoagulation in patients with HCM, given the high incidence of stroke, prophylactic anticoagulation is recommended in all patients with HCM and AF (if no contraindication).[1] A direct oral anticoagulant is recommended first-line option, and a vitamin K antagonist (e.g., warfarin) second-line option.[1] [2] [98] See New-onset atrial fibrillation (Management) and Chronic atrial fibrillation (Management)

Symptomatic sinus node dysfunction

Permanent pacemaker implantation is indicated as in other forms of heart disease. Permanent pacemaker implantation is also indicated for patients with high-grade atrioventricular (AV) block who are symptomatic, or who have arrhythmias such as AF or ventricular arrhythmias that are worsened by bradycardia or prolonged pauses.

Systolic and/or diastolic dysfunction

While patients can have LVOTO and reduced cardiac function, this is uncommon. Patients with systolic and/or diastolic dysfunction with a significant obstructive component should have their therapy tailored to prevent worsening LVOTO. These patients require individualised therapy with specialist management.

Symptomatic patients: predominantly non-obstructive with preserved systolic function

Symptoms are related to diastolic dysfunction, with impaired filling resulting in reduced output and pulmonary congestion. Patients are more symptomatic when heart rate is higher, as diastolic filling is further compromised; a negative chronotropic agent may therefore be beneficial in this setting.[4]

Non-dihydropyridine calcium-channel blockers are thought to improve symptoms, secondary to their beneficial effect on myocardial relaxation and ventricular filling. They are also negative inotropes, which may aid in relief of symptoms. Beta-blockers may be used, as they may improve diastolic filling due to their negative chronotropic effect. Disopyramide is not recommended, as it may decrease cardiac output more than the other therapies in this setting.

Oral nitrates can be used cautiously for relief of angina.[1] Ranolazine can be considered to improve symptoms in patients with angina-like chest pain and no evidence of left ventricular outflow tract obstruction, even in the absence of obstructive coronary artery disease.[1] See Stable ischaemic heart disease (Management) for further details of management of angina.

Management of heart failure with reduced ejection fraction is focused on: (1) risk stratification and management of comorbidities, including hypertension, diabetes mellitus, obesity, atrial fibrillation, coronary artery disease, chronic kidney disease, and obstructive sleep apnoea; (2) non-pharmacological management, including exercise and weight loss; and (3) pharmacological treatment, namely disease-modifying medications and medication for symptom management (e.g., relief of congestion with loop diuretics).[99] For further details of management of heart failure, see Heart failure with preserved ejection fraction (Management)

Management of complications

- If the patient develops symptoms or signs of ischaemia, decreasing myocardial oxygen demand with negative inotropic and chronotropic agents may prove beneficial. Aetiology of the ischaemia should be identified (i.e., increased LV outflow tract obstruction, coronary artery disease, or myocardial bridging).
- In addition, all patients with symptomatic ventricular arrhythmias or important asymptomatic ventricular arrhythmias should receive an ICD.[2]
- Atrial arrhythmias (e.g., AF) should be treated (as described for patients with predominant LVOTO) to maintain sinus rhythm. The risk of systemic thromboembolism in these patients is thought to be significant, and thus the threshold for initiation of anticoagulant therapy should be low.[2] Anticoagulation is recommended for all patients with HCM and AF, with a direct oral anticoagulant first-line, and a vitamin K antagonist (e.g., warfarin) second-line.[2]
- Permanent pacemaker implantation is indicated in patients with symptomatic sinus node dysfunction and HCM, and in patients with high-grade AV block who are symptomatic, or who have arrhythmias such as AF or ventricular arrhythmias that are worsened by bradycardia or prolonged pauses.

Symptomatic patients: end-stage heart failure with systolic dysfunction

The average duration from onset of symptoms to end-stage disease is 14 years.[100] Systolic function deteriorates, and the left ventricle remodels and becomes dilated. The mechanism of end-stage HCM is likely to be diffuse ischaemic injury. Risk factors for end-stage disease include younger age at diagnosis,

more severe symptoms, larger LV cavity size, and family history of end-stage disease. Mortality is high once this complication develops, with mean time to death or cardiac transplantation of 2.7 ± 2.1 years.[100]

Medical therapy

These patients are treated with standard heart failure therapy, including initially a beta-blocker and ACE inhibitor or angiotensin-II receptor antagonist.[101]

Second-line therapies include digoxin, diuretics, or aldosterone antagonists. Diuretics should be used cautiously in these patients compared with patients with other causes of heart failure, due to possible impairment in preload. Digoxin may be used in a patient with a dilated LV with reduced function. It is not typically used in the setting of severe hypertrophy. Digoxin should not be used if the patient has ventricular pre-excitation through an accessory pathway, as its AV nodal blocking effect may promote rapid conduction of the atrial arrhythmia across the accessory pathway, precipitating a ventricular arrhythmia or haemodynamic compromise.

Heart transplantation

If patients remain refractory to medical therapy, they should be referred for consideration for heart transplant.[101] Heart transplants have been shown to improve survival and quality of life for patients with end-stage heart failure secondary to HCM.[101] Presence of comorbidities, caretaker status, and goals of care should all be taken into account when considering patient eligibility for transplant.[101]

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Initial (summary)		
asymptomatic		
at high risk of sudden death	**1st**	**implantable cardioverter-defibrillator (ICD) + avoidance of high-intensity athletics**
not at high risk of sudden death	**1st**	**observation**

Acute (summary)		
symptomatic: predominant left ventricular outflow tract obstruction (LVOTO) with preserved systolic function		
	1st	negative inotropic and chronotropic agents
	adjunct	mavacamten
	adjunct	implantable cardioverter-defibrillator (ICD)
	adjunct	management of arrhythmias
	adjunct	surgical coronary artery unroofing (selected cases)
	2nd	myectomy/alcohol septal ablation/dual-chamber pacing
	adjunct	implantable cardioverter-defibrillator (ICD)
	adjunct	management of arrhythmias
	adjunct	surgical coronary artery unroofing (selected cases)
symptomatic: predominant non-obstructive with preserved systolic function		
	1st	negative inotropic and chronotropic agents
	adjunct	management of angina
	adjunct	management of heart failure
	adjunct	implantable cardioverter-defibrillator (ICD)
	adjunct	management of arrhythmias
	adjunct	surgical coronary artery unroofing (selected cases)

Ongoing		(summary)
symptomatic: end-stage heart failure with systolic dysfunction		
	1st	beta-blocker + ACE inhibitor/angiotensin-II receptor antagonist + consideration for implantable cardioverter-defibrillator + avoidance of high-intensity athletics
	adjunct	digoxin
	adjunct	diuretics
	adjunct	aldosterone antagonists
	adjunct	management of arrhythmias
	adjunct	surgical coronary artery unroofing (selected cases)
	adjunct	referral for heart transplant

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Initial

asymptomatic

at high risk of sudden death — **1st** — **implantable cardioverter-defibrillator (ICD) + avoidance of high-intensity athletics**

» Guidelines recommend ICD placement for patients with hypertrophic cardiomyopathy (HCM) and previous documented cardiac arrest or sustained ventricular arrhythmia causing syncope or haemodynamic compromise in the absence of reversible causes.[1] [2] Routine diagnostic testing to evaluate the risk of sudden death is recommended, regardless of symptom status. European guidelines recommend comprehensive sudden cardiac death risk stratification in all patients at initial presentation, then at 1-2 year intervals or whenever there is a change in clinical status.[1]

» Prophylactic ICD placement should also be considered in selected asymptomatic patients including those with one or more first-degree or close relatives 50 years of age or less with sudden death presumably caused by HCM, patients with a maximum left ventricular (LV) wall thickness greater than or equal to 30 mm, patients with one or more recent episodes of syncope suspected to be arrhythmic, LV apical aneurysm, LV systolic dysfunction with ejection fraction <50%, and late gadolinium enhancement >15% on cardiac magnetic resonance imaging.[1] [2]

» No randomised controlled trials studying the effect of ICD placement have been performed in patients with HCM, although there is evidence from observational studies.[2][68] Complications following ICD placement have been reported to occur at a rate of 3.4% per year.[69] Sports with high likelihood of bodily collision should also be avoided after ICD implant.[70]

» Patients and carers should be fully informed and participate in decision-making regarding ICD placement.[2] They should be counselled on the risk of inappropriate shocks, implant complications, and the social, occupational, and driving implications of the device. Implantation of a cardioverter defibrillator is only recommended in patients who have an expectation of good-quality survival >1 year.[1]

Initial

not at high risk of sudden death — **1st** — **observation**

» If the patient is not considered at high risk of sudden death, implantable cardioverter-defibrillator placement is not required. Patients in this category who are asymptomatic should be closely observed for the development of hypertrophic cardiomyopathy. Routine diagnostic testing to evaluate the risk of sudden death is recommended, regardless of symptom status. European guidelines recommend comprehensive sudden cardiac death risk stratification in all patients at initial presentation, then at 1-2 year intervals or whenever there is a change in clinical status.[1]

» US and European guidelines now advise that for those who are genotype-positive and phenotype-negative (asymptomatic without evidence of left ventricular hypertrophy on cardiac imaging), participation in competitive sport of any intensity is reasonable.[2] [65]

» Patients should be regularly assessed for change in clinical status.

Acute

symptomatic: predominant left ventricular outflow tract obstruction (LVOTO) with preserved systolic function

1st **negative inotropic and chronotropic agents**

Primary options

» atenolol: 50-100 mg orally once daily

OR

» propranolol: 80-160 mg orally (sustained-release) once daily

OR

» metoprolol: 100-450 mg/day orally (immediate-release) given in 2-3 divided doses

OR

» nadolol: 40 mg orally once daily initially, increase by 40-80 mg/day increments every 3-7 days according to response, maximum 240 mg/day

Secondary options

» verapamil: consult specialist for guidance on dose

OR

» diltiazem: consult specialist for guidance on dose

Tertiary options

» atenolol: 50-100 mg orally once daily
-or-
» propranolol: 80-160 mg orally (sustained-release) once daily
-or-
» metoprolol: 100-450 mg/day orally (immediate-release) given in 2-3 divided doses
-or-
» nadolol: 40 mg orally once daily initially, increase by 40-80 mg/day increments every 3-7 days according to response, maximum 240 mg/day
-or-

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» verapamil: consult specialist for guidance on dose
-or-
» diltiazem: consult specialist for guidance on dose
--AND--
» disopyramide: <50 kg body weight: 200 mg orally (controlled-release) twice daily; >50 kg body weight: 300 mg orally (controlled-release) twice daily

» A symptomatic patient with resting or provocable LVOTO is initially treated with negative inotropic or chronotropic therapy to help alleviate obstruction. Tachyphylaxis to medication is common, and medication dosage must be adjusted over time. In the absence of many randomised controlled trials, pharmacological therapy is mostly administered on an empirical basis to improve functional capacity and reduce symptoms.[1]

» Beta-blockers are beneficial due to their negative inotropic and chronotropic properties. Non-vasodilating beta-blockers are considered first-line therapy for symptomatic HCM due to LVOTO. In standard doses, they are usually well tolerated. Reported side effects include fatigue, impotence, sleep disturbances, and bradycardia. Substantial experience suggests that beta-blockers can mitigate symptoms and reduce outflow tract obstruction in those patients with LVOTO occurring with exercise. There is little evidence to suggest a beneficial effect on resting outflow tract gradients; however, one small RCT found that metoprolol reduced LVOTO obstruction at rest and during exercise, provided symptom relief, and improved quality of life in patients with obstructive HCM. Maximum exercise capacity remained unchanged.[71] [72] Beta-blocker therapy may also be of benefit in patients with HCM and symptoms suggestive of ischaemia. Patients with co-existing ischaemia should have their beta-blocker dosing optimised.

» Non-dihydropyridine calcium-channel blockers (diltiazem, verapamil) are used for relief of symptoms, including those with a component of chest pain.[2] Verapamil and diltiazem have vasodilating properties as well as negative inotropic and chronotropic effects.[2] Short-term oral administration may increase exercise capacity, improve symptoms, and normalise or improve LV diastolic filling without altering systolic function.[1] Verapamil can be used when beta-blockers are contraindicated or ineffective. Diltiazem should be considered in patients

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who are intolerant or have contraindications to beta-blockers and verapamil.[1] Caution in administration of non-dihydropyridine calcium-channel blockers is advised, because if the vasodilatory properties predominate, outflow tract obstruction may be increased, resulting in pulmonary oedema and shock. They should be avoided if a patient has pronounced obstruction or elevated pulmonary arterial pressure.[1]

» Disopyramide is a negative inotrope and a type IA anti-arrhythmic agent. For patients with LVOTO and persistent severe symptoms despite therapy with beta-blockers or non-dihydropyridine calcium-channel blockers, adding disopyramide is recommended.[2] Disopyramide is often used in combination with an agent that has atrioventricular nodal blocking properties, as it may increase the ventricular rate in patients with atrial fibrillation. It may be considered as monotherapy in patients who are intolerant to or have contraindications to beta-blockers and verapamil or diltiazem.[1] Dose-limiting anticholinergic side effects include dry eyes and mouth, urinary hesitancy or retention, and constipation. The ECG QT interval should be monitored for prolongation.[1]

» Consensus recommendations have previously restricted all athletes with HCM from all competitive sports; however, US and European guidelines now advise that participation in high-intensity exercise/competitive sports may be considered for some individuals after comprehensive evaluation and shared discussion.[2] [65]

adjunct **mavacamten**

Treatment recommended for SOME patients in selected patient group

Primary options

» mavacamten: 2.5 to 15 mg orally once daily
Only initiate therapy in patients with left ventricular ejection fraction (LVEF) ≥55%. Titrate dose according to LVEF and Valsalva left ventricular outflow tract (LVOT) gradient. Interrupt treatment if LVEF <50%. See prescribing information for more information.

» Mavacamten is a cardiac myosin inhibitor approved for the treatment of adults with symptomatic New York Heart Association class II-III obstructive hypertrophic cardiomyopathy (HCM) to improve functional capacity and

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symptoms.[1] [74] [75] It works by inhibiting cardiac myosin adenosine triphosphatase (ATPase), thus reducing actin-myosin cross-bridge formation; this reduces contractility and improves myocardial dynamics.[1]

» While mavacamten is approved for this indication in the US, the most recent guidelines from the American Heart Association and American College of Cardiology do not include a cardiac myosin inhibitor in the treatment cascade.[2] Mavacamten is currently available in the US through a Risk Evaluation and Mitigation Strategy (REMS) programme, designed to monitor patients periodically with echocardiograms for early detection of systolic dysfunction and to screen for drug interactions prior to each prescription.[76]

» European and UK guidelines now recommend mavacamten as a second-line treatment for patients with HCM and LVOTO.[1] [75] It should be considered when optimal medical therapy with beta-blockers, calcium-channel blockers, and/or disopyramide is ineffective or poorly tolerated. European guidelines stipulate that in the absence of evidence to the contrary, mavacamten should not be used with disopyramide, but may be coadministered with beta-blockers or calcium-channel blockers.[1] UK guidelines differ, stating that it can be added-on to individually optimised standard care that includes beta-blockers, calcium-channel blockers, or disopyramide, unless these are contraindicated.[75]

» In patients with contraindications or known sensitivity to beta-blockers, calcium-channel blockers, and disopyramide, mavacamten may be considered as monotherapy.[1]

» Up-titration of medication to a maximum tolerated dose should be monitored in accordance with licensed recommendations using echocardiographic surveillance of LV ejection fraction.[1]

adjunct **implantable cardioverter-defibrillator (ICD)**

Treatment recommended for SOME patients in selected patient group

» Patients should be considered for an ICD if at any stage during therapy they are found to be at a higher risk level, or develop new symptomatic or important asymptomatic ventricular arrhythmias.

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» Guidelines recommend ICD placement for patients with hypertrophic cardiomyopathy (HCM) and previous documented cardiac arrest or sustained ventricular tachycardia.[1] [2] Routine diagnostic testing to evaluate the risk of sudden death is recommended, regardless of symptom status. European guidelines recommend comprehensive sudden cardiac death risk stratification in all patients at initial presentation, then at 1-2 year intervals or whenever there is a change in clinical status.[1]

» A single marker of high risk for sudden cardiac arrest may also be sufficient to consider ICD placement in selected patients.[1] [2][68] Patients in whom this would apply include those with one or more first-degree or close relatives 50 years of age or less with sudden death presumably caused by HCM, patients with a maximum LV wall thickness greater than or equal to 30 mm, patients with one or more recent, unexplained episodes of syncope suspected to be arrhythmic, LV apical aneurysm, LV systolic dysfunction with ejection fraction <50%, and late gadolinium enhancement >15% on cardiac magnetic resonance imaging.[1] [2]

» No randomised controlled trials studying the effect of ICD placement have been performed in patients with HCM, although there is evidence from observational studies.[2] [68]

» Complications following ICD placement have been reported to occur at a rate of 3.4% per year.[69] Contact sports should be avoided after ICD implant.[70] Patients and carers should be fully informed and participate in decision-making regarding ICD placement.[2] They should be counselled on the risk of inappropriate shocks, implant complications, and the social, occupational, and driving implications of the device. Implantation of a cardioverter defibrillator is only recommended in patients who have an expectation of good-quality survival >1 year.[1]

adjunct **management of arrhythmias**

Treatment recommended for SOME patients in selected patient group

» Atrial arrhythmias, including atrial fibrillation (AF), are common, particularly in older patients with hypertrophic cardiomyopathy (HCM). Prevalence of AF among patients with HCM is estimated at 17% to 39%, with an annual incidence of 2.8% to 4.8%.[1] AF is often poorly tolerated in patients with HCM.[2] As a result, an aggressive strategy for maintaining sinus rhythm is warranted.

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» Paroxysmal and chronic AF are linked to left atrial enlargement.[4] AF is independently associated with heart-failure-related death, occurrence of fatal and non-fatal stroke, as well as long-term progression of heart failure symptoms.[2]

» Management of AF is as per patients without HCM. However, digoxin is not typically used for atrial rate control if the patient has significant hypertrophy, as there is a theoretical concern that it could exacerbate LVOTO due to a positive inotropic effect.[2] In addition, traditional stroke risk scoring systems used in the general population, such as CHA2DS2-VASc (congestive heart failure or left ventricular dysfunction, hypertension, age ≥75 [doubled], diabetes, stroke [doubled]-vascular disease, aged 65-74 years, sex category [female]) are not predictive in patients with HCM, with evidence suggesting that they may perform suboptimally.[1] [2] [98] For this reason, although there are no randomised controlled trials evaluating the role of anticoagulation in patients with HCM, given the high incidence of stroke, prophylactic anticoagulation is recommended in all patients with HCM and AF (if no contraindication).[1] A direct oral anticoagulant is recommended first-line option, and a vitamin K antagonist (e.g., warfarin) second-line option.[1] [2] [98] See New-onset atrial fibrillation (Management) and Chronic atrial fibrillation (Management)

» Permanent pacemaker implantation is indicated in patients with symptomatic sinus node dysfunction and HCM, and in patients with high-grade atrioventricular block who are symptomatic, or who have arrhythmias such as AF or ventricular arrhythmias that are worsened by bradycardia or prolonged pauses.[2]

» All patients with symptomatic ventricular arrhythmias or important asymptomatic ventricular arrhythmias should receive an implantable cardioverter-defibrillator (ICD).[1] [2] In patients with HCM and pacing-capable ICDs, programming antitachycardia pacing is recommended to minimise risk of shocks.[2] Although data are lacking, anti-arrhythmic drugs such as beta-blockers (e.g., sotalol) and amiodarone should be considered for patients with recurrent, symptomatic ventricular arrhythmia, or recurrent ICD shocks.[1] Catheter ablation in specialised centres may be considered in select patients with recurrent, symptomatic sustained monomorphic VT (SMVT) or recurrent ICD shocks for SMVT, in

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whom anti-arrhythmic drugs are ineffective, contraindicated, or not tolerated.[1] [2]

adjunct **surgical coronary artery unroofing (selected cases)**

Treatment recommended for SOME patients in selected patient group

» In the presence of ischaemia due to a myocardial bridge (a band of heart muscle lying on top of a coronary artery) surgical coronary artery unroofing of the myocardial bridge has been shown to lead to resolution of ischaemia and of ventricular arrhythmias in some patients, and may lessen the incidence of sudden death.[30] [94] However, the evidence for the benefit of this procedure is limited and risks of the procedure need to be considered.[96]

2nd **myectomy/alcohol septal ablation/dual-chamber pacing**

» Surgical myectomy (septal reduction therapy) is the optimal procedure for relief of drug-refractory LVOTO in patients with hypertrophic cardiomyopathy (HCM).[20] [30] Indicated if severe symptoms persist despite medical therapy, with a resting or provocable outflow tract gradient of ≥50 mmHg.[2] European guidelines specify that patients should be in New York Heart Association/Ross functional class III-IV, or be experiencing recurrent exertional syncope due to LVOTO, despite maximum tolerated medical therapy.[1]

» Myectomy abolishes or substantially reduces LV outflow tract gradients in over 90% of cases, reduces systolic anterior motion-related mitral regurgitation, and improves exercise capacity and symptoms. Long-term symptomatic benefit is achieved in >80% of patients, with a long-term survival comparable to that of the general population. Preoperative determinants of a good long-term outcome are: age <50 years; left atrial size <46 mm; absence of AF; and male sex.[1] Older age and increased severity of comorbidities are predictive of poor surgical outcomes.[83] Data from experienced centres suggest that institutions should aim for mortality rates of <1%.[2]

» Alcohol septal ablation (ASA) is an alternative to surgery in adults with HCM. It involves the delivery of alcohol into a target septal perforator branch of the left anterior descending coronary artery, for the purpose of producing a myocardial infarction and reducing septal thickness.[1] Septal remodelling and relief of obstruction after

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ASA occurs over several months, resulting in a smaller reduction in resting gradient compared with surgical myectomy, but a similar reduction in patient symptoms.[85] [86]

» Complications include ventricular arrhythmias (2.2%), coronary dissection (1.8%), and complete heart block (>10%) necessitating permanent pacemaker placement.[87] There is an increased need for permanent pacemaker implantation post-procedure compared with surgical myectomy.[88]

» Neither ASA or surgical myectomy have been conclusively shown to affect the incidence of sudden death. While randomised controlled trial data comparing the later outcomes of both procedures are lacking, a retrospective, observational study compared long-term mortality of patients with obstructive HCM following septal myectomy or ASA. It concluded that ASA was associated with increased long-term all-cause mortality compared with septal myectomy. This finding remained after adjustment for confounding factors (patients undergoing ASA tend to be older with more comorbidities and reduced septal thickness compared to patients undergoing septal myectomy), but may still be influenced by unmeasured confounders.[90] Results of each procedure are likely to be dependent on the technical expertise of the centre where the procedure is to be performed.[86]

» Dual-chamber pacing may be an option in select patients with medically refractory symptomatic obstruction who are not candidates for, or who do not desire, surgery or ASA. It is not a primary line of therapy; however, as efficacy is unproven in randomised cross-over blinded studies.[91] [92] Randomised trials have not demonstrated benefit in objective measures of exercise capacity. Gradient reduction is less than that achieved with surgery.[93]

» Consensus recommendations have previously restricted all athletes with HCM from all competitive sports; however, US and European guidelines now advise that participation in high-intensity exercise/competitive sports may be considered for some individuals after comprehensive evaluation and shared discussion.[2] [65]

adjunct **implantable cardioverter-defibrillator (ICD)**

Treatment recommended for SOME patients in selected patient group

Acute

» Patients should be considered for an ICD if at any stage during therapy they are found to be at a higher risk level, or develop new symptomatic or important asymptomatic ventricular arrhythmias.

» Guidelines recommend ICD placement for patients with hypertrophic cardiomyopathy (HCM) and previous documented cardiac arrest or sustained ventricular tachycardia.[1][2] Routine diagnostic testing to evaluate the risk of sudden death is recommended, regardless of symptom status. European guidelines recommend comprehensive sudden cardiac death risk stratification in all patients at initial presentation, then at 1-2 year intervals or whenever there is a change in clinical status.[1]

» A single marker of high risk for sudden cardiac arrest may also be sufficient to consider ICD placement in selected patients.[1] [2][68] Patients in whom this would apply include those with one or more first-degree or close relatives 50 years of age or less with sudden death presumably caused by HCM, patients with a maximum LV wall thickness greater than or equal to 30 mm, patients with one or more recent, unexplained episodes of syncope suspected to be arrhythmic, LV apical aneurysm, LV systolic dysfunction with ejection fraction <50%, and late gadolinium enhancement >15% on cardiac magnetic resonance imaging.[1][2]

» No randomised controlled trials studying the effect of ICD placement have been performed in patients with HCM, although there is evidence from observational studies.[2] [68]

» Complications following ICD placement have been reported to occur at a rate of 3.4% per year.[69] Contact sports should be avoided after ICD implant.[70] Patients and carers should be fully informed and participate in decision-making regarding ICD placement.[2] They should be counselled on the risk of inappropriate shocks, implant complications, and the social, occupational, and driving implications of the device. Implantation of a cardioverter defibrillator is only recommended in patients who have an expectation of good-quality survival >1 year.[1]

adjunct **management of arrhythmias**

Treatment recommended for SOME patients in selected patient group

» Atrial arrhythmias, including atrial fibrillation (AF), are common, particularly in older patients with hypertrophic cardiomyopathy (HCM).

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Prevalence of AF among patients with HCM is estimated at 17% to 39%, with an annual incidence of 2.8% to 4.8%.[1] AF is often poorly tolerated in patients with HCM.[2] As a result, an aggressive strategy for maintaining sinus rhythm is warranted.

» Paroxysmal and chronic AF are linked to left atrial enlargement.[4] AF is independently associated with heart-failure-related death, occurrence of fatal and non-fatal stroke, as well as long-term progression of heart failure symptoms.[2]

» Management of AF is as per patients without HCM. However, digoxin is not typically used for atrial rate control if the patient has significant hypertrophy, as there is a theoretical concern that it could exacerbate LVOTO due to a positive inotropic effect.[2] In addition, traditional stroke risk scoring systems used in the general population, such as CHA2DS2-VASc (congestive heart failure or left ventricular dysfunction, hypertension, age ≥75 [doubled], diabetes, stroke [doubled]-vascular disease, aged 65-74 years, sex category [female]) are not predictive in patients with HCM, with evidence suggesting that they may perform suboptimally.[1] [2] [98] For this reason, although there are no randomised controlled trials evaluating the role of anticoagulation in patients with HCM, given the high incidence of stroke, prophylactic anticoagulation is recommended in all patients with HCM and AF (if no contraindication).[1] A direct oral anticoagulant is recommended first-line option, and a vitamin K antagonist (e.g., warfarin) second-line option.[1] [2] [98] See New-onset atrial fibrillation (Management) and Chronic atrial fibrillation (Management)

» Permanent pacemaker implantation is indicated in patients with symptomatic sinus node dysfunction and HCM, and in patients with high-grade atrioventricular block who are symptomatic, or who have arrhythmias such as AF or ventricular arrhythmias that are worsened by bradycardia or prolonged pauses.[2]

» All patients with symptomatic ventricular arrhythmias or important asymptomatic ventricular arrhythmias should receive an implantable cardioverter-defibrillator (ICD).[1] [2] In patients with HCM and pacing-capable ICDs, programming antitachycardia pacing is recommended to minimise risk of shocks.[2] Although data are lacking, anti-arrhythmic drugs such as beta-blockers (e.g., sotalol) and amiodarone should be considered for

Acute

patients with recurrent, symptomatic ventricular arrhythmia, or recurrent ICD shocks.[1] Catheter ablation in specialised centres may be considered in select patients with recurrent, symptomatic sustained monomorphic VT (SMVT) or recurrent ICD shocks for SMVT, in whom anti-arrhythmic drugs are ineffective, contraindicated, or not tolerated.[1] [2]

adjunct **surgical coronary artery unroofing (selected cases)**

Treatment recommended for SOME patients in selected patient group

» In the presence of ischaemia due to a myocardial bridge (a band of heart muscle lying on top of a coronary artery) surgical coronary artery unroofing of the myocardial bridge has been shown to lead to resolution of ischaemia and of ventricular arrhythmias in some patients, and may lessen the incidence of sudden death.[30] [94] However, the evidence for the benefit of this procedure is limited and risks of the procedure need to be considered.[96]

symptomatic: predominant non-obstructive with preserved systolic function

1st **negative inotropic and chronotropic agents**

Primary options

» atenolol: 50-100 mg orally once daily

OR

» propranolol: 80-160 mg orally (sustained-release) once daily

OR

» metoprolol: 100-450 mg/day orally (immediate-release) given in 2-3 divided doses

OR

» nadolol: 40 mg orally once daily initially, increase by 40-80 mg/day increments every 3-7 days according to response, maximum 240 mg/day

OR

MANAGEMENT

Acute

» verapamil: consult specialist for guidance on dose

OR

» diltiazem: consult specialist for guidance on dose

» Symptoms are related to diastolic dysfunction, with impaired filling resulting in reduced output and pulmonary congestion. Patients are more symptomatic when heart rate is higher, as diastolic filling is further compromised; a negative chronotropic agent may therefore be beneficial in this setting.[4]

» Non-dihydropyridine calcium-channel blockers (verapamil and diltiazem) are thought to improve symptoms secondary to the beneficial effect on myocardial relaxation and ventricular filling. They are also negative inotropes, which may aid in relief of symptoms.

» Beta-blockers may be used, as they may improve diastolic filling due to their negative chronotropic effect. Beta-blocker therapy may also be of benefit in patients with HCM and symptoms suggestive of ischaemia.

» Disopyramide is not recommended, as it may decrease cardiac output more than the other therapies in this setting.

» Consensus recommendations have previously restricted all athletes with HCM from all competitive sports; however, US and European guidelines now advise that participation in high-intensity exercise/competitive sports may be considered for some individuals after comprehensive evaluation and shared discussion.[2] [65]

adjunct **management of angina**

Treatment recommended for SOME patients in selected patient group

» Oral nitrates can be used cautiously for relief of angina.[1] Ranolazine can be considered to improve symptoms in patients with angina-like chest pain and no evidence of left ventricular outflow tract obstruction, even in the absence of obstructive coronary artery disease.[1]

» See Stable ischaemic heart disease (Management) for further details of management of angina.

adjunct **management of heart failure**

Acute

Treatment recommended for SOME patients in selected patient group

» Management of heart failure with reduced ejection fraction is focused on: (1) risk stratification and management of comorbidities, including hypertension, diabetes mellitus, obesity, atrial fibrillation, coronary artery disease, chronic kidney disease, and obstructive sleep apnoea; (2) non-pharmacological management, including exercise and weight loss; and (3) pharmacological treatment, namely disease-modifying medications and medication for symptom management (e.g., relief of congestion with loop diuretics).[99]

» For further details of management of heart failure, see Heart failure with preserved ejection fraction (Management)

adjunct **implantable cardioverter-defibrillator (ICD)**

Treatment recommended for SOME patients in selected patient group

» Patients should be considered for an ICD if at any stage during therapy they are found to be at a higher risk level, or develop new symptomatic or important asymptomatic ventricular arrhythmias.

» Guidelines recommend ICD placement for patients with hypertrophic cardiomyopathy (HCM) and previous documented cardiac arrest or sustained ventricular tachycardia.[1] [2] Routine diagnostic testing to evaluate the risk of sudden death is recommended, regardless of symptom status. European guidelines recommend comprehensive sudden cardiac death risk stratification in all patients at initial presentation, then at 1-2 year intervals or whenever there is a change in clinical status.[1]

» A single marker of high risk for sudden cardiac arrest may also be sufficient to consider ICD placement in selected patients.[1] [2][68] Patients in whom this would apply include those with one or more first-degree or close relatives 50 years of age or less with sudden death presumably caused by HCM, patients with a maximum LV wall thickness greater than or equal to 30 mm, patients with one or more recent, unexplained episodes of syncope suspected to be arrhythmic, LV apical aneurysm, LV systolic dysfunction with ejection fraction <50%, and late gadolinium enhancement >15% on cardiac magnetic resonance imaging.[1] [2]

Acute

» No randomised controlled trials studying the effect of ICD placement have been performed in patients with HCM, although there is evidence from observational studies.[2] [68]

» Complications following ICD placement have been reported to occur at a rate of 3.4% per year.[69] Contact sports should be avoided after ICD implant.[70] Patients and carers should be fully informed and participate in decision-making regarding ICD placement.[2] They should be counselled on the risk of inappropriate shocks, implant complications, and the social, occupational, and driving implications of the device. Implantation of a cardioverter defibrillator is only recommended in patients who have an expectation of good-quality survival >1 year.[1]

»

adjunct **management of arrhythmias**

Treatment recommended for SOME patients in selected patient group

» Atrial arrhythmias, including atrial fibrillation (AF), are common, particularly in older patients with hypertrophic cardiomyopathy (HCM). Prevalence of AF among patients with HCM is estimated at 17% to 39%, with an annual incidence of 2.8% to 4.8%.[1] AF is often poorly tolerated in patients with HCM.[2] As a result, an aggressive strategy for maintaining sinus rhythm is warranted.

» Paroxysmal and chronic AF are linked to left atrial enlargement.[4] AF is independently associated with heart-failure-related death, occurrence of fatal and non-fatal stroke, as well as long-term progression of heart failure symptoms.[2]

» Management of AF is as per patients without HCM. However, digoxin is not typically used for atrial rate control if the patient has significant hypertrophy, as there is a theoretical concern that it could exacerbate LVOTO due to a positive inotropic effect.[2] In addition, traditional stroke risk scoring systems used in the general population, such as CHA2DS2-VASc (congestive heart failure or left ventricular dysfunction, hypertension, age ≥75 [doubled], diabetes, stroke [doubled]-vascular disease, aged 65-74 years, sex category [female]) are not predictive in patients with HCM, with evidence suggesting that they may perform suboptimally.[1] [2] [98] For this reason, although there are no randomised controlled trials evaluating the role of anticoagulation in patients with HCM,

Acute

given the high incidence of stroke, prophylactic anticoagulation is recommended in all patients with HCM and AF (if no contraindication).[1] A direct oral anticoagulant is recommended first-line option, and a vitamin K antagonist (e.g., warfarin) second-line option.[1] [2] [98] See New-onset atrial fibrillation (Management) and Chronic atrial fibrillation (Management)

» Permanent pacemaker implantation is indicated in patients with symptomatic sinus node dysfunction and HCM, and in patients with high-grade atrioventricular block who are symptomatic, or who have arrhythmias such as AF or ventricular arrhythmias that are worsened by bradycardia or prolonged pauses.[2]

» All patients with symptomatic ventricular arrhythmias or important asymptomatic ventricular arrhythmias should receive an implantable cardioverter-defibrillator (ICD).[1] [2] In patients with HCM and pacing-capable ICDs, programming antitachycardia pacing is recommended to minimise risk of shocks.[2] Although data are lacking, anti-arrhythmic drugs such as beta-blockers (e.g., sotalol) and amiodarone should be considered for patients with recurrent, symptomatic ventricular arrhythmia, or recurrent ICD shocks.[1] Catheter ablation in specialised centres may be considered in select patients with recurrent, symptomatic sustained monomorphic VT (SMVT) or recurrent ICD shocks for SMVT, in whom anti-arrhythmic drugs are ineffective, contraindicated, or not tolerated.[1] [2]

adjunct **surgical coronary artery unroofing (selected cases)**

Treatment recommended for SOME patients in selected patient group

» In the presence of ischaemia due to a myocardial bridge (a band of heart muscle lying on top of a coronary artery) surgical coronary artery unroofing of the myocardial bridge has been shown to lead to resolution of ischaemia and of ventricular arrhythmias in some patients, and may lessen the incidence of sudden death.[30] [94] However, the evidence for the benefit of this procedure is limited and risks of the procedure need to be considered.[96]

Ongoing

symptomatic: end-stage heart failure with systolic dysfunction

1st **beta-blocker + ACE inhibitor/angiotensin-II receptor antagonist + consideration for implantable cardioverter-defibrillator + avoidance of high-intensity athletics**

Primary options

» metoprolol: 12.5 to 200 mg orally (extended-release) once daily
-or-
» bisoprolol: 1.25 to 10 mg orally once daily
--AND--
» captopril: 6.25 to 50 mg orally three times daily
-or-
» enalapril: 2.5 to 20 mg orally twice daily
-or-
» fosinopril: 5-40 mg orally once daily
-or-
» lisinopril: 2.5 to 40 mg orally once daily
-or-
» perindopril: 2-16 mg orally once daily
-or-
» quinapril: 5-20 mg orally twice daily
-or-
» ramipril: 1.25 to 10 mg orally once daily
-or-
» trandolapril: 1-4 mg orally once daily

Secondary options

» metoprolol: 12.5 to 200 mg orally (extended-release) once daily
-or-
» bisoprolol: 1.25 to 10 mg orally once daily
--AND--
» candesartan: 4-32 mg orally once daily
-or-
» losartan: 25-100 mg orally once daily
-or-
» valsartan: 40-160 mg orally twice daily

» The average duration from onset of symptoms to end-stage disease is 14 years.[100] Systolic function deteriorates, and the left ventricle remodels and becomes dilated. The mechanism of end-stage HCM is likely to be diffuse ischaemic injury. Risk factors for end-stage disease include younger age at diagnosis, more severe symptoms, larger left ventricular cavity size, and family history of end-stage disease.

Ongoing

» Mortality is high once this complication develops, with mean time to death or cardiac transplantation of 2.7 ± 2.1 years.[100]

» These patients are treated with standard heart failure therapy, including initially a beta-blocker and ACE inhibitor or angiotensin-II receptor antagonist. Other medications may be necessary as adjunctive therapies.

» Patients should be considered for an implantable cardioverter-defibrillator if at any stage during therapy they are found to be at a higher risk level, or develop new symptomatic or important asymptomatic ventricular arrhythmias.

» Patients should refrain from high-intensity athletics.

adjunct **digoxin**

Treatment recommended for SOME patients in selected patient group

Primary options

» digoxin: 0.125 to 0.5 mg orally once daily

» Digoxin can be used in patients with a dilated left ventricle with reduced function. It is not used typically in the setting of severe hypertrophy. Digoxin should not be used if the patient has ventricular pre-excitation through an accessory pathway, as its atrioventricular nodal blocking effect may promote rapid conduction of the atrial arrhythmia across the accessory pathway, precipitating a ventricular arrhythmia or haemodynamic compromise.

» Digoxin levels need monitoring. Toxicity may occur especially if there is renal dysfunction, hypokalaemia, hypomagnesaemia, or hypothyroidism.

adjunct **diuretics**

Treatment recommended for SOME patients in selected patient group

Primary options

» furosemide: 20-80 mg/dose orally initially, increase by 20-40 mg/dose increments every 6-8 hours according to response, maximum 600 mg/day

OR

Ongoing

» bumetanide: 0.5 to 1 mg orally once or twice daily initially, increase according to response, maximum 10 mg/day

Secondary options

» chlorothiazide: 250-500 mg orally once or twice daily, maximum 1000 mg/day

OR

» hydrochlorothiazide: 25 mg orally once or twice daily, increase according to response, maximum 200 mg/day

OR

» metolazone: 2.5 to 20 mg orally once daily

» Diuretics should be considered for patients who have evidence of, or a prior history of, fluid retention.

» Amiloride and triamterene should be used with caution with aldosterone antagonists, because of the increased risk of developing hyperkalaemia. Close monitoring of serum potassium levels is suggested in this situation.

adjunct **aldosterone antagonists**

Treatment recommended for SOME patients in selected patient group

Primary options

» spironolactone: 25-100 mg orally once daily

Secondary options

» eplerenone: 25-50 mg orally once daily

» Aldosterone antagonists may be used in patients with moderate to severe heart failure. These agents should be used with caution in patients with renal dysfunction and hyperkalaemia.

» Patients should discontinue potassium repletion, and renal function and serum potassium levels require strict monitoring.

adjunct **management of arrhythmias**

Treatment recommended for SOME patients in selected patient group

» Atrial arrhythmias, including atrial fibrillation (AF), are common, particularly in older patients with hypertrophic cardiomyopathy (HCM).

Ongoing

Prevalence of AF among patients with HCM is estimated at 17% to 39%, with an annual incidence of 2.8% to 4.8%.[1] AF is often poorly tolerated in patients with HCM.[2] As a result, an aggressive strategy for maintaining sinus rhythm is warranted.

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Ongoing

patients with recurrent, symptomatic ventricular arrhythmia, or recurrent ICD shocks.[1] Catheter ablation in specialised centres may be considered in select patients with recurrent, symptomatic sustained monomorphic VT (SMVT) or recurrent ICD shocks for SMVT, in whom anti-arrhythmic drugs are ineffective, contraindicated, or not tolerated.[1] [2]

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Treatment recommended for SOME patients in selected patient group

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adjunct **referral for heart transplant**

Treatment recommended for SOME patients in selected patient group

» If patients remain refractory to medical therapy, they should be referred for consideration for heart transplant surgery.[101]

» Heart transplants have been shown to improve survival and quality of life for patients with end-stage heart failure secondary to hypertrophic cardiomyopathy.[101] Presence of comorbidities, caretaker status, and goals of care should all be taken into account when considering patient eligibility for transplant.[101]

Emerging

Research into genotype-phenotype correlation

Studies are ongoing to identify other disease-causing mutations and disease-modifying factors for HCM. This research may serve by improving genotype-phenotype correlations and prognosis or may aid in the discovery of therapies that can prevent or alter disease progression in gene-positive individuals. A small study found that pre-clinical sarcomere mutations were associated with more prominently abnormal left ventricular relaxation, ECG changes, mitral leaflet length, and serum pro-B-type natriuretic peptide concentrations in people who went on to develop HCM.[102] Another study found that patients with diagnosed HCM and mutations in the MYBPC3 gene, which encodes cardiac myosin binding protein C, were more likely to have impaired ventricular function and were possibly more prone to arrhythmic events than those without MYBPC3 mutations.[103]

Aficamten

Aficamten is a next-in-class cardiac myosin inhibitor with a shorter half-life than mavacamten.[104] In a phase 2 clinical trial, high-dose aficamten was generally well tolerated and was associated with a 93% response rate (defined as a final resting left ventricular outflow tract [LVOT] gradient ≤30 mmHg and Valsalva LVOT gradient ≤50 mmHg) compared to 8% with placebo.[105] Additional trials investigating the long-term safety and tolerability of aficamten, as well as its efficacy in patients with obstructive HCM, are ongoing. The Food and Drug Administration has granted breakthrough therapy and orphan drug designation to aficamten for patients with obstructive HCM.

Secondary prevention

Screening of all first-degree family members with echocardiography, ECG, and clinical follow-up is required.

All patients with HCM should:

- Be counseled about exercise (see Patient discussions).
- Undergo serial testing with echocardiogram, Holter monitor, exercise testing, and clinical evaluation to determine their risk level for sudden cardiac death (SCD); implantable cardioverter-defibrillators are indicated for prevention of SCD in selected individuals at higher risk.
- Be considered for anticoagulation for stroke prevention if they develop atrial fibrillation.
- Be referred for consideration of surgical coronary unroofing if they develop ischaemia due to myocardial bridging.

Patient discussions

Patients should return for routine lifelong follow-up and seek medical attention for symptoms of exertional chest pain, dyspnoea, palpitations, presyncope, or syncope.

Advice should be given about exercise; whereas historical guidelines have focused predominantly on elite young athletes and provided prohibitive recommendations, it is now well recognised that exercise is beneficial to cardiovascular health, and light and moderate exercise should be encouraged in all able individuals with hypertrophic cardiomyopathy (HCM). All patients with HCM, if able, should adhere to the current minimal physical activity recommendations of 150 minutes of moderate exercise per week divided over five sessions; those who are not able should perform symptom-limited physical activity. Moderate exercise appears to be safe.[112] US and European guidelines now advise that participation in high-intensity exercise/competitive sports may be considered for some individuals after comprehensive evaluation and shared discussion with an expert.[2] [65] This evaluation should consider symptomatic status, family history, functional capacity, cardiac morphology, and risk profile. A full complement of cardiac investigations is recommended, including an echocardiogram, exercise stress test, cardiovascular magnetic resonance, and prolonged ECG monitor.[112]

Screening of family members should be discussed. All first-degree relatives of patients with cardiomyopathy should be offered clinical screening with ECG and cardiac imaging (echocardiogram and/or cardiac MRI). In families in whom a disease-causing genetic variant has been identified, cascade genetic testing should be offered. Those relatives who have the familial genetic variant(s) should undergo regular clinical evaluation (every 1-3 years before the age of 60 years, and then every 3-5 years thereafter) with ECG, multimodality cardiac imaging, and additional investigations (e.g., Holter monitoring) as required. Those relatives without a phenotype who do not have the same disease-causing variant as the proband are discharged from further follow-up but advised to seek re-assessment if they develop symptoms or if new clinically relevant data emerge in the family. When no pathogenic variant is identified in the proband or genetic testing is not performed, regular, long-term clinical evaluation using a multiparametric approach that includes ECG and cardiac imaging should be considered in first-degree relatives. During cascade screening, where a first-degree relative has died, clinical evaluation of close relatives of the deceased individual (i.e., second-degree relatives of the index patient) should be considered.[1]

Clinical psychological support for patients and their families affected by inherited cardiomyopathies is an important aspect of the multi-disciplinary team's care approach and should be available as required.[1]

FOLLOW UP

Monitoring

Monitoring

In general, patients with cardiomyopathy require lifelong follow-up to evaluate changes in symptoms, risk of adverse events, ventricular function, and cardiac rhythm.[1] A shared approach between cardiomyopathy units and general cardiologists is strongly recommended.[1]

All patients should undergo clinical assessment and risk stratification at the time of diagnosis and at 1-2 year intervals, or whenever there is a change in clinical status.[1] [2] Such evaluation should include: a detailed family history, with particular emphasis on whether other family members with hypertrophic cardiomyopathy experienced premature death; a detailed history with enquiry into symptoms of chest pain, palpitations, or loss of consciousness; echocardiography; Holter monitoring; ECG; and exercise testing.[2] Cardiac magnetic resonance evaluation should be considered every 2-5 years or more frequently in patients with progressive disease.[1]

Patients with risk factors for sudden death, including non-sustained ventricular tachycardia on sequential Holter monitorings, previous cardiac arrest, extreme hypertrophy, and unexplained syncope, should be closely monitored; implantable cardioverter-defibrillator placement should be considered. See Diagnostic approach for more information on risk stratification.

Frequent follow-up at 6-month intervals is recommended for those with high-risk features for sudden cardiac death (SCD) and focused on mitigation of risk. It is important to note that the European Society of Cardiology risk score was developed from cohort studies of non-athletes and it is difficult to ascertain whether the risk of SCD is further exacerbated by the stressors associated with high-intensity activities.[38] Therefore, further or more frequent screening strategies may be indicated in those participating in high-intensity athletic activities, especially those that are highly dynamic start-stop type exercises. Patients over 65 years of age may have additional prevalent cardiac comorbidities such as hypertension and diabetes that may increase their risk.[111]

Complications

Complications	Timeframe	Likelihood
deterioration of clinical condition during pregnancy	**short term**	**medium**
Pregnancy and vaginal delivery are generally well tolerated in women with hypertrophic cardiomyopathy who are asymptomatic without significant left ventricular outflow tract obstruction (LVOTO). Expert maternal/fetal medical specialist care is recommended for women on medical therapy as the medications may have adverse effects in the fetus. Expert maternal/fetal medical specialist care is also recommended for women who are symptomatic or have LVOTO >50 mmHg as symptoms may worsen due to changes in contractility, heart rate, and vascular resistance or venous capacitance that occur with pregnancy, labour, and/or delivery.[109] [110]		
sudden death	**short term**	**low**
Sudden cardiac death (SCD) is the most common mode of death in young people with hypertrophic cardiomyopathy (HCM), occurring with an incidence of 1% per year.[67] The proposed mechanism of SCD is ventricular tachycardia secondary to ischaemia.[4] SCD typically occurs in the setting of extreme exertion. Risk factors for HCM sudden death include: younger age; non-sustained ventricular tachycardia on Holter monitor; abnormal BP response to exercise; massive hypertrophy (left ventricular wall thickness ≥30 mm); severe outflow obstruction on echocardiogram; family history of sudden death; personal history of unexplained syncope; prior cardiac arrest or sustained ventricular tachycardia; left ventricular systolic dysfunction with ejection fraction <50%; left atrial enlargement; presence of left ventricular apical aneurysm; diffuse and extensive late gadolinium enhancement by cardiac MRI.[1] [2] [40] HCM patients who survived a cardiac arrest and were treated with conventional medical therapy or surgery have been shown to have a 7-year mortality rate of 33%.[29]		
infective endocarditis (IE)	**short term**	**low**
The site of the vegetation is usually the thickened anterior mitral valve leaflet. Hypertrophic cardiomyopathy no longer mandates antibiotic IE prophylaxis unless there is a history of prior endocarditis or prosthetic valve.		
ischaemic stroke	**short term**	**low**
Atrial fibrillation in hypertrophic cardiomyopathy (HCM) significantly increases the risk of stroke caused by systemic emboli.[4] Anticoagulation is recommended for patients with HCM and atrial fibrillation, with direct oral anticoagulants first-line and vitamin K antagonists (e.g., warfarin) second-line.[2]		
atrial fibrillation	**variable**	**high**
Atrial arrhythmias, including atrial fibrillation, are particularly common in older patients with hypertrophic cardiomyopathy (HCM). Prevalence of atrial fibrillation among patients with HCM is estimated at 17% to 39%, with an annual incidence of 2.8% to 4.8%.[1] It is often poorly tolerated in patients with HCM.[2]		

FOLLOW UP

Prognosis

In the majority of cases, hypertrophic cardiomyopathy (HCM) carries a benign prognosis. At presentation 90% of patients will be asymptomatic, and the majority of those will remain asymptomatic on long-term follow-up. In one prospective study, the onset of any symptom was delayed until the patient was 70 years or older in 18% of patients.[10] Patients presenting with mild to moderate symptoms typically experience slow progression of symptoms with advancing age.

A subgroup of patients (5% of all HCM patients and 30% of tertiary referral populations) will develop symptomatic outflow tract obstruction that is refractory to medical therapy. Patients with resting provocable left ventricular (LV) outflow gradients >50 mmHg and severe limiting symptoms are candidates for surgical or catheter intervention.[2]

In patients who are asymptomatic at presentation, the annual mortality rate is lower than in those patients with symptoms (0.9% vs. 1.9%). Similarly, the annual rate of sudden death is lower in patients without symptoms at presentation (0.1% vs. 1.4%).[106] See Diagnostic approach for information about risk factors for sudden death.

The annual mortality rate for those patients diagnosed in childhood is substantially greater than that of the general population (1.3% vs. 0.08%). In contrast, the annual mortality rate for those diagnosed in adulthood is not significantly increased above the general population (2.2% vs. 1.9%).[107]

End-stage heart failure develops in around 2% to 15% of people with HCM and carries a poor prognosis.[108] Systolic function deteriorates, and the left ventricle remodels and becomes dilated. The mechanism of end-stage HCM is likely to be diffuse ischaemic injury. Risk factors for end-stage disease include younger age at diagnosis, more severe symptoms, larger LV cavity size, and family history of end-stage disease. Mortality is high once symptomatic heart failure develops, with mean time to death or cardiac transplantation of 2.7 ± 2.1 years.[100]

Diagnostic guidelines

Europe

ESC Guidelines for the management of cardiomyopathies (https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Cardiomyopathy-Guidelines)

Published by: European Society of Cardiology **Last published:** 2023

North America

Recommendations for multimodality cardiovascular imaging of patients with hypertrophic cardiomyopathy (https://www.asecho.org/ase-guidelines-by-publication-date)

Published by: American Society of Echocardiography; American Society of Nuclear Cardiology; Society for Cardiovascular Magnetic Resonance; Society of Cardiovascular Computed Tomography **Last published:** 2022

2020 AHA/ACC guideline for the diagnosis and treatment of hypertrophic cardiomyopathy (https://professional.heart.org/en/guidelines-and-statements)

Published by: American Heart Association; American College of Cardiology **Last published:** 2020

Noninvasive risk stratification techniques for identifying patients at risk for sudden cardiac death (https://professional.heart.org/en/guidelines-and-statements)

Published by: American Heart Association; American College of Cardiology Foundation; Heart Rhythm Society **Last published:** 2008

Oceania

Diagnosis and management of hypertrophic cardiomyopathy - position statement (https://www.csanz.edu.au/for-professionals/position-statements-and-practice-guidelines)

Published by: Cardiac Society of Australia and New Zealand **Last published:** 2016

Treatment guidelines

Europe

ESC Guidelines for the management of cardiomyopathies (https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Cardiomyopathy-Guidelines)

Published by: European Society of Cardiology **Last published:** 2023

2021 ESC guidelines on cardiac pacing and cardiac resynchronization therapy (https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines)

Published by: European Society of Cardiology; European Heart Rhythm Association **Last published:** 2021

2020 ESC guidelines on sports cardiology and exercise in patients with cardiovascular disease (https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines)

Published by: European Society of Cardiology **Last published:** 2020

Recommendations for participation in competitive and leisure time sport in athletes with cardiomyopathies, myocarditis, and pericarditis (https://academic.oup.com/eurheartj/article/40/1/19/5248228)

Published by: European Association of Preventive Cardiology **Last published:** 2019

North America

2020 AHA/ACC guideline for the diagnosis and treatment of hypertrophic cardiomyopathy (https://professional.heart.org/en/guidelines-and-statements)

Published by: American Heart Association; American College of Cardiology **Last published:** 2020

2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities (https://professional.heart.org/en/guidelines-and-statements)

Published by: American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines; Heart Rhythm Society **Last published:** 2012

Oceania

Diagnosis and management of hypertrophic cardiomyopathy - position statement (https://www.csanz.edu.au/for-professionals/position-statements-and-practice-guidelines)

Published by: Cardiac Society of Australia and New Zealand **Last published:** 2016

Key articles

- Arbelo E, Protonotarios A, Gimeno JR, et al. 2023 ESC Guidelines for the management of cardiomyopathies. Eur Heart J. 2023 Oct 1;44(37):3503-626. Full text (https://academic.oup.com/eurheartj/article/44/37/3503/7246608?login=false) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/37622657?tool=bestpractice.bmj.com)

- Ommen SR, Mital S, Burke 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. Circulation. 2020 Dec 22;142(25):e558-631. Full text (https://www.ahajournals.org/doi/10.1161/CIR.0000000000000937) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/33215931?tool=bestpractice.bmj.com)

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Images

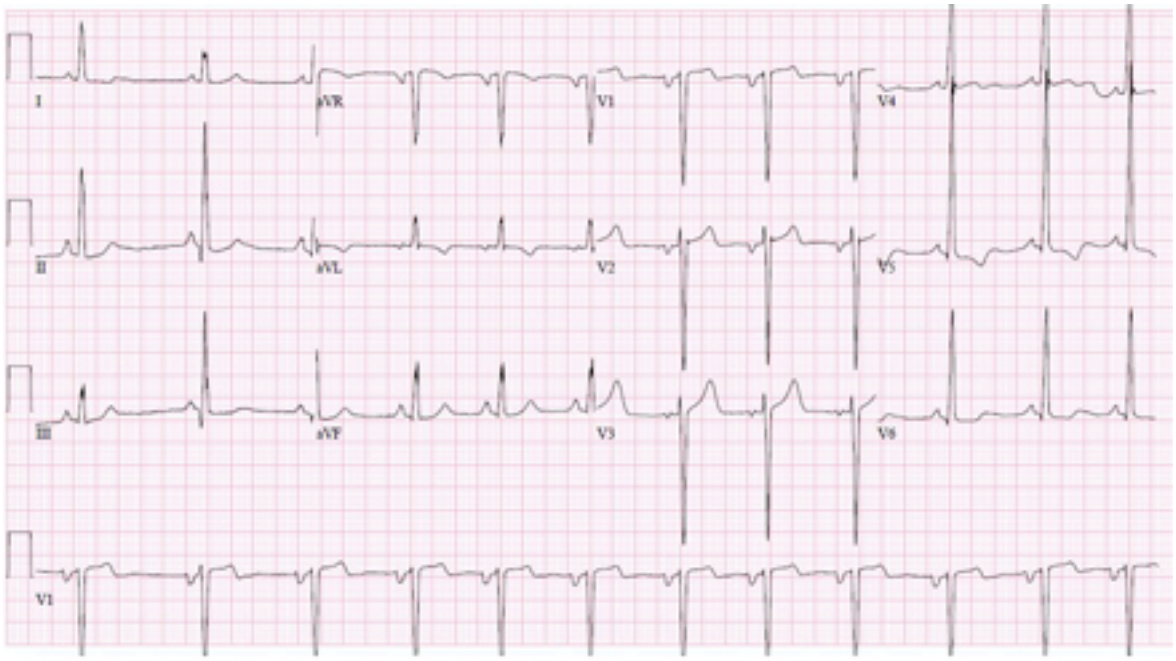

Figure 1: ECG showing changes associated with LVH

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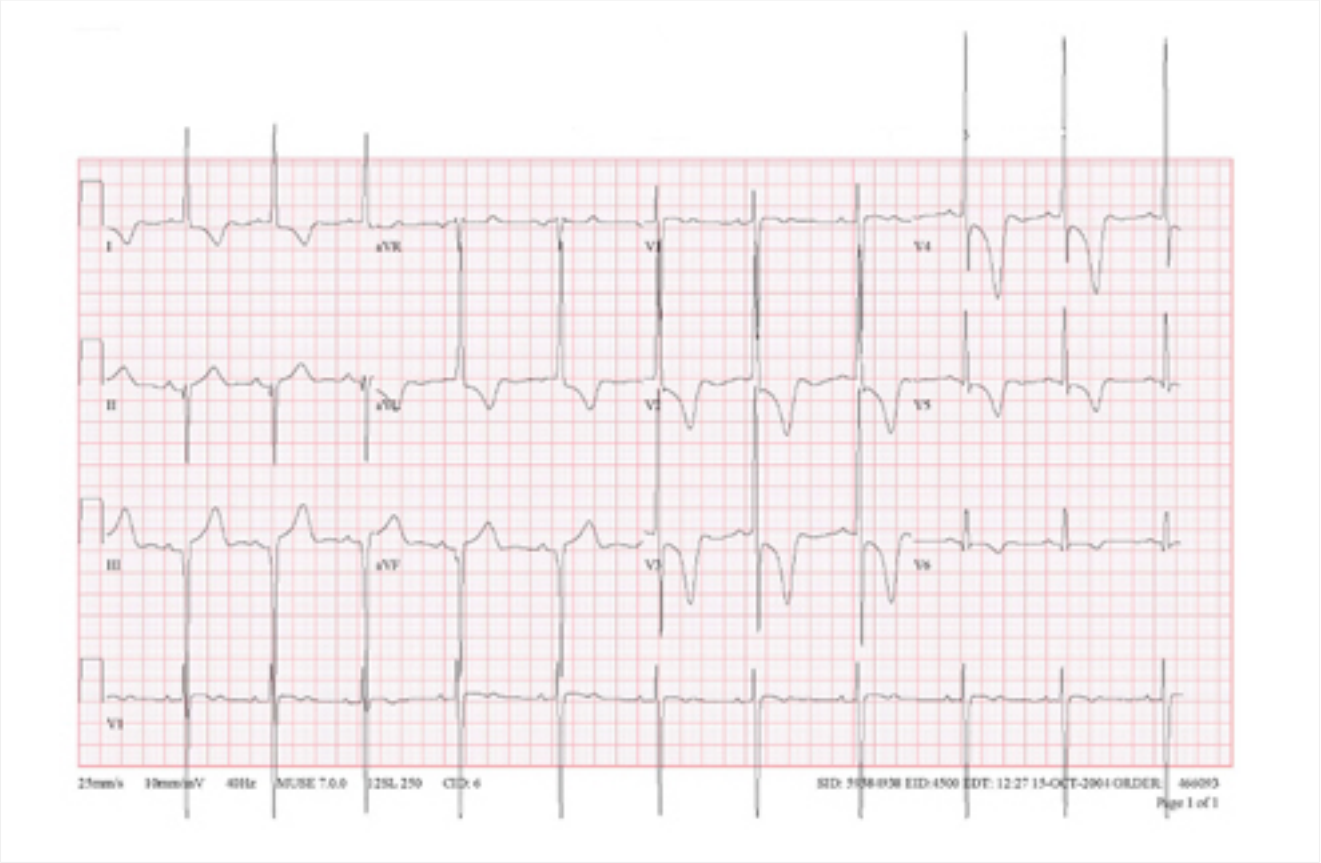

Figure 2: Giant T-wave inversion

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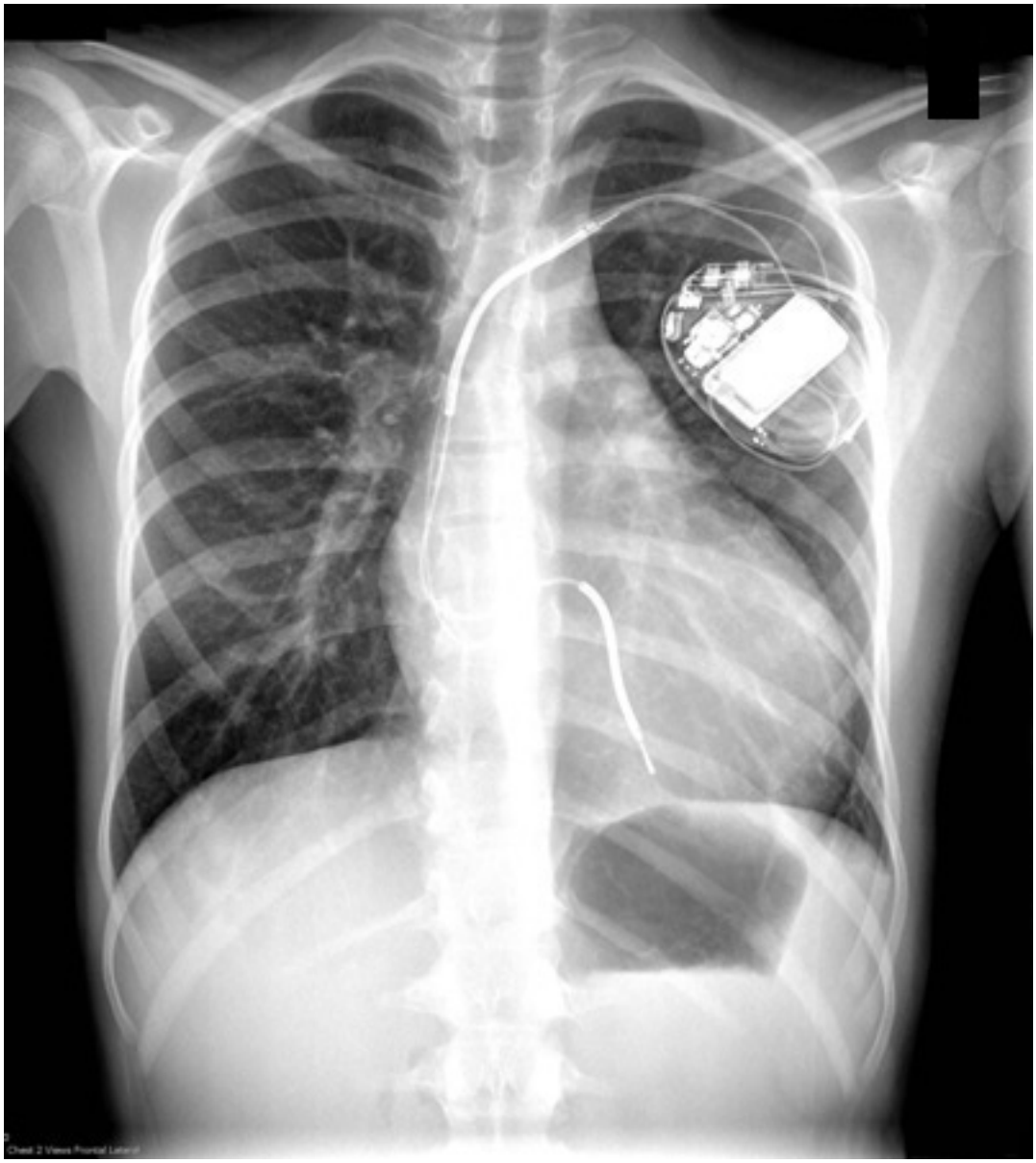

Figure 3: CXR of a patient with HCM demonstrating cardiomegaly

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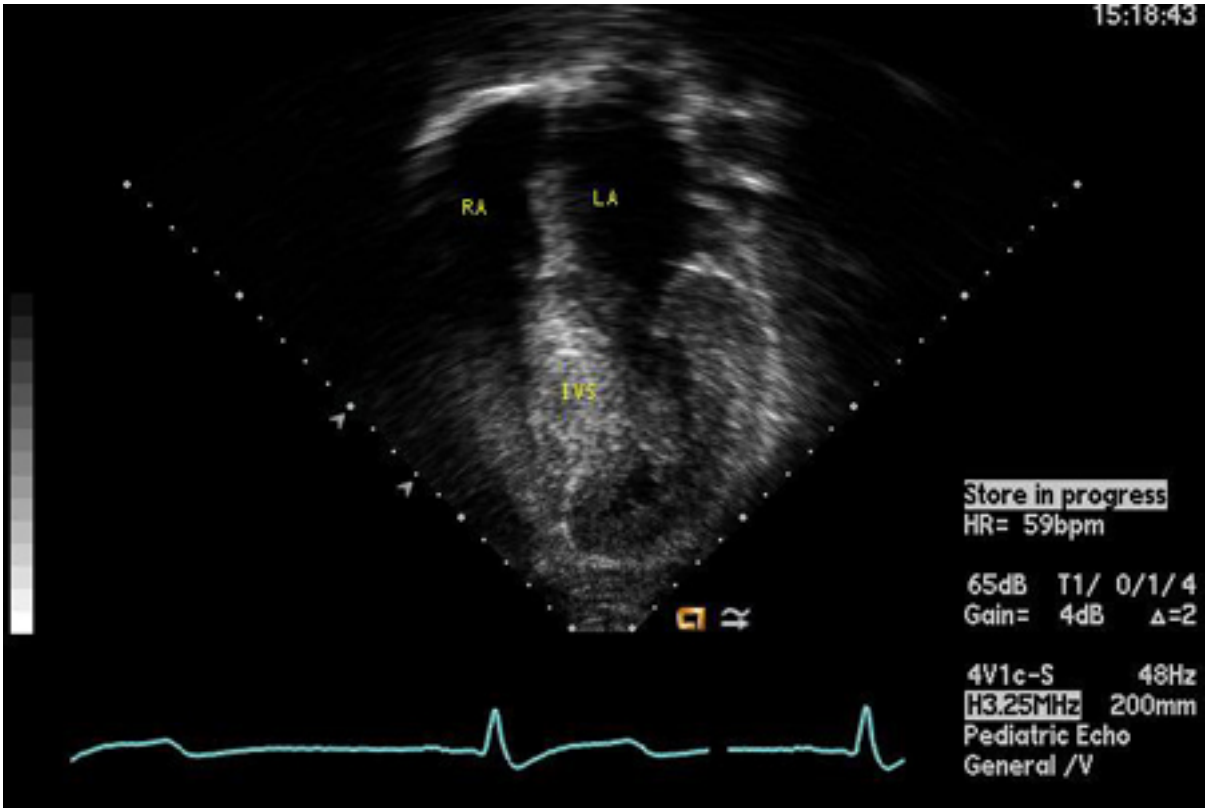

Figure 4: Apical 4-chamber image demonstrating hypertrophy of the interventricular septum

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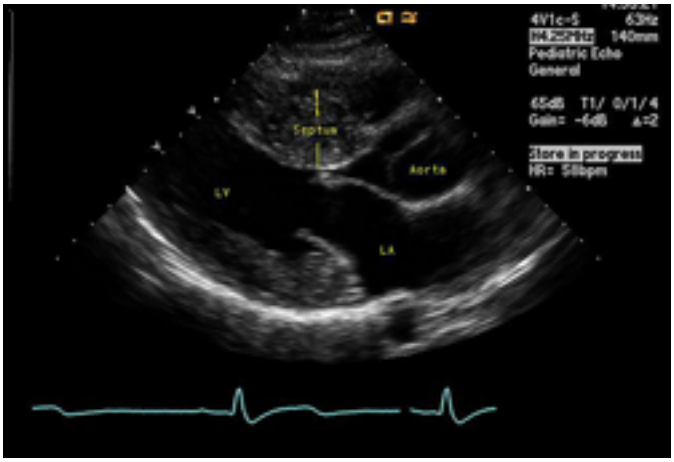

Figure 5: Long axis echocardiography view - asymmetrical septal hypertrophy

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Figure 1 – BMJ Best Practice Numeral Style

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DISCLOSURES: TA serves as a steering committee member/local investigator and his institution has received research funding for hypertrophic cardiomyopathy-related clinical trials sponsored by Bristol Myers Squibb; Cytokinetics Inc.; Tenaya Pharmaceuticals; and Imbria Pharmaceuticals.

// Acknowledgements:

Dr Theodore Abraham would like to gratefully acknowledge Dr Monica Mukherjee, Dr Melanie D. Everitt, and Dr Anji T. Yetman, previous contributors to this topic.
DISCLOSURES: MM, MDE, and ATY declare that they have no competing interests.

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