# HYPERTROPHIC CARDIOMYOPATHY

## Definition

Hypertrophic cardiomyopathy (HCM) is a genetic disorder characterized by hypertrophy of the left ventricle in the absence of haemodynamic stress and loading conditions, such as hypertension or valvular disease, that are sufficient to account for the degree of hypertrophy.[1, 2] Typically, HCM is usually recognized by maximal LV wall thickness >15 mm in one or more LV myocardial segments, with wall thickness of 13 to 14 mm considered borderline.[2] A threshold of a z-score >2.5 (where z-score is the number of standard deviations from the population mean) may be appropriate to identify early HCM in asymptomatic children with no family history, whereas for children with a definitive family history or a positive genetic test, a threshold of a z-score >2 may suffice for early diagnosis.[2]

Other typical findings such as LV wall thickness >=15 mm due to basal septal hypertrophy with myocyte disarray, LVOT obstruction with gradient >=30 mm Hg at rest or exercise (labile obstruction), and mitral valve systolic anterior motion, are common but not obligatory for a diagnosis of HCM. There are several patterns of hypertrophy, such asymmetrical septal hypertrophy with or without LVOT obstruction, midventricular hypertrophy, apical hypertrophy, LV free wall hypertrophy, posterobasal left ventricular free wall hypertrophy, segmental hypertrophy with normal LV mass on MRI, and, rarely, concentric hypertrophy similar to that found in systemic hypertension.[3, 4]

AHA/ACC use the term HCM only for unexplained LV hypertrophy, ie hypertrophy that is not caused by detectable metabolic or storage disease in the context of multisystem disorders such as RASopathies (variants in several genes involved in RAS-MAPK signaling), mitochondrial myopathies, glycogen/lysosomal storage diseases in children, and Fabry, amyloid, sarcoid, hemochromatosis, Danon cardiomyopathy in adults.[2] In these diseases, although the magnitude and distribution of increased LV wall thickness can be similar to that of isolated HCM caused by variants in sarcomeric genes, the pathophysiologic mechanisms responsible for hypertrophy, natural history, and treatment strategies are not the same.

## Epidemiology

HCM is the most common genetic cardiomyopathy. The prevalence of the disorder has been traditionally considered as 1 in 500 people, but it may be higher.[1, 5] There is a lower incidence in children and a small male preponderance. The prevalence of HCM in phenotype-negative children relatives at risk of developing HCM is 6% at 12 years follow-up.[6]

# Aetiology

Pathogenic variation in genes encoding proteins of the cardiac sarcomere, and mainly 8 **sarcomeric protein genes,** is responsible for 30%–40% of cases of hypertrophic cardiomyopathy.[7, 8] Inheritance is autosomal dominant; every offspring has a 50% chance of developing the disease later in life (age-dependent penetrance), but with considerable heterogeneity in phenotypic expression and clinical course. [4, 9, 10] However, recent studies have highlighted the contribution of AR inheritance, particularly in populations with more prevalent consanguinity.[7] Patients with new mutations (ie without any relatives with the disease) or without any evidence of a genetic aetiology to their disease, also exist. Familial disease is less frequent in children than in adults, with various modes of inheritance. Table 1 and Figure 1 present the most common genes implicated in HOCM (see also Appendix 2). Mutations in MYH7 and MYBPC3 that encode for the β-myosin heavy chain and the myosin binding protein C are responsible for 60-80% % of sarcomeric protein gene mutations. Other sarcomere-related genes, such as FHOD3, are also implicated.[11] Truncating variants of alpha-protein kinase 3 (*ALPK3*) that participates in intercalated disc and sarcomere structural organization, may cause a severe form of HCM.[12] Bi-allelic truncating variants Most of mutations are missence (substitution of one aminoacid by another), but insertion/delete mutations may also occur. Heterogenous expression of these mutations as well as modifier genes and environmental factors contribute to the characteristic diversity of HCM phenotype. The reasons for the development of hypertrophy due to sarcomeric mutations are not clear and the same genes may be responsible for dilated or other forms of cardiomyopathies. Reduced contractile function and activation of various signaling pathways are speculated.

Nonmendelian genetic variants with reproducible moderate-effect sizes and low penetrance, intermediate-effect variants, also influence disease severity and outcomes, particularly when combined with monogenic disease-causing variants. Intermediate-effect variants in **non-sarcomere genes** with moderate to strong association with HCM have been described.[7] Overall, variants in these nonsarcomeric genes such as *ALPK3*, *CSRP3*, *FHOD3*, and *TRIM63*, are estimated to account for 5% to 10% of HCM cases.[13] Sarcomere-negative HCM may also be polygenic and multifactorial with lower rates of heart failure, sudden death, atrial fibrillation, and stroke.[14] Metabolic storage diseases, and mitochondrial disease may also result in similar cardiac hypertrophy. However, genetic variation in the majority of non-sarcomeric genes implicated in HCM is not associated with the condition, and the aetiology of the condition is unknown in many patients.[15]

Left ventricular hypertrophy in the context of childhood neuropathy, corneal opacities, proteinuria, hearing loss, and small vascular lesions on the buttocks suggest **Anderson-Fabry disease** (deficiency of a-galactosidase) that can be treated with primary

enzyme replacement. [16] Other **lysosomal and glycagon storage diseases** such Danon disease may also produce similar LV hypertrophy.[17] **Danon disease** (X-linked lysosome-associated membrane protein cardiomyopathy) is highly lethal and requires early recognition and referral for transplantation. **Friedreich ataxia** is an autosomal recessive neurodegenerative disease caused by a defect in the gene encoding for the mitochondrial protein frataxin.[18] Myocardial involvement is well documented, with concentric left ventricular hypertrophy as the dominating cardiac finding. Average life expectancy in patients with Friedreich ataxia and cardiac involvement is considerably reduced to 29-38 years.[19] **Mitochondrial disease** includes clinical disorders that occur as a result of dysfunctional cellular oxidative phosphorylation due to defects in mitochondrial (or rarely nuclear) DNA. Symmetrical LV hypertrophy not fulfilling standard criteria for HCM and organ involvement, such as diabetes and deafness, suggest the possibility of mitochondrial DNA disease.[20] **Cardiac amyloidosis** may also result in concentric or asymmetrical LV hypertrophy. Most cases of left ventricular hypertrophy in children are associated with congenital malformations, inherited metabolic disorders, and neuromuscular diseases.

## Pathophysiology

Left ventricular hypertrophy is typically characterized by myocyte disarray with cardiomyocytes varying in size and shape, and forming abnormal intercellular connections usually with expansion of the interstitial compartment and areas of replacement fibrosis.[21] There is also small vessel disease, in which intramural coronary vessels are apparently narrowed by medial hypertrophy.[21] Myocyte disarray is characteristic but not confined to HCM. It can be seen in patients with other diseases such Noonan's syndrome, Friedreich's ataxia, and congenital disorders.

Systolic septal bulging into the LVOT, and hyperdynamic LV contraction (causing the Venturi effect) contribute to creation of a variable ***LVOT gradient*** that increases with decreased afterload. Approximately 25% of patients have dynamic LVOT obstruction caused by contact between the anterior, or less commonly the posterior, mitral valve leaflet and the interventricular septum during systole (***systolic anterior motion-SAM***). Severe LV hypertrophy results in increased chamber stiffness and diastolic dysfunction. Intrinsic abnormalities of the mitral apparatus, including fibrous leaflet thickening, prolapse, and malposition of the anterior papillary muscle, occur in an estimated 20% of patients with HCM, and contribute to the obstruction. CMR may also detect mitral leaflet elongation that is independent of other disease variables.[22] Muscular mitral-aortic discontinuity with displacement of the anterior mitral leaflet toward the ventricular apex can be identified in young patients, suggesting that a functionally elongated anterior leaflet, may contribute to

outflow tract obstruction.[23] Thus ***mitral regurgitation*** may be primary or due to SAM. Dyspnea occurs with exertion and may result from limitation of cardiac output due to the low end-diastolic volume of a noncompliant LV, high pulmonary venous pressure due to diastolic dysfunction, and mitral regurgitation.

***Myocardial ischaemia*** and angina may result from compression of the microcirculation, LVOT obstruction, and impaired ventricular relaxation, in the context of high myocardial oxygen demand by the hypertrophied myocardium associated with elevated LV systolic pressure.[24] ***Atrial fibrillation or flutter*** are associated with a worsening of symptoms because these patients are depended on atrial transport due to the concomitant diastolic dysfunction, an important pathophysiological feature of HCM. Pre-syncopal episodes and syncope are due to LVOT obstruction, myocardial ischemia, inappropriate systemic vasodilation, and ventricular arrhythmias. Myocardial fibrosis and, especially, disarray are most probably the arrhythmogenic substrates. Abnormal blood pressure response during exercise, defined as fall or failure to rise >20 mm Hg, may be seen in up to 25% of patients with HCM, and is attributed to ***autonomic dysfunction***. Left ventricular ***systolic dysfunction*** develops in approximately 8% of patients with HCM with pathogenic sarcomeric variants (particularly in thin filament genes).[25] Impaired LV compliance from hypertrophy and fibrosis, microvascular ischemia, and delayed inactivation from abnormal intracellular calcium reuptake are features of HCM that contribute to ***diastolic dysfunction.***

A subset of patients with HCM have associated ***ventricular preexcitation***, which can be due to atrioventricular accessory pathways or fasciculoventricular fibers. The prevalence of preexcitation is 10× higher in patients with underlying storage disease and 5× higher in patients with underlying metabolic disease than in patients with isolated HCM.[26]

## Presentation and Natural History

Patients may be asymptomatic or present with dyspnea and angina with a characteristic day to day variation in the activity needed to cause symptoms. Presyncope or syncope may also be the presenting symptom and is a marker for risk of sudden death.

There are 3 relatively discrete, but not mutually exclusive pathways, of clinical progression:

1. ***Sudden cardiac death*** (SCD) due to unpredictable ventricular tachyarrhythmias, most commonly in young asymptomatic patients <35 years of age (including competitive athletes). The estimated rate of SCD is 0.5-1% per year in the overall HCM population. Sex is not a major determinant of the risk of SCD. Most events, even in athletes, are not related to strenuous exercise.
2. ***Heart failure*** characterized by exertional dyspnea, with or without chest pain, that may be progressive despite preserved systolic function and sinus rhythm. In a small

proportion of patients, heart failure may progress to the end stage with LV remodeling and systolic dysfunction caused by extensive myocardial scarring. Abrupt onset of congestive heart failure is uncommon and should raise suspicion of other, superimposed cardiac disease, such as light-chain amyloidosis.[27]

3. ***Atrial fibrillation***, either paroxysmal or chronic, also associated with various degrees of heart failure and an increased risk of systemic thromboembolism and both fatal and nonfatal stroke.

4. ***Ventricular tachycardia*** rather than VF is the most common arrhythmia in patients with HCM. It is amenable to antitachycardia pacing and is associated with lower LV ejection fraction and higher LV diameters.[28]

Patients with childhood-onset HCM are more likely to have sarcomeric disease, carry a higher risk of life-threatening ventricular arrhythmias, and have greater need for advanced heart failure therapies.[29] Approximately 10% of patients with HCM will develop end-stage morphology with LV dilation and wall thinning, that is associated with worse outcome.[30] Patients surviving into the *seventh decade* with this genetic disease are at low risk for HCM-related mortality and morbidity, including sudden death (even when conventional risk factors are present).[31] The incidence of ventricular arrhythmias declines with age, but the risk for heart failure and atrial fibrillation increases, becoming most prevalent by mid- to late adulthood, even in patients diagnosed before 40 years of age.[32] *Women* with HCM present at more advanced age, with more symptoms, worse cardiopulmonary exercise tolerance, and more echocardiographic evidence of diastolic dysfunction and obstructive physiology than men.[33] *Thin filament mutations* are associated with increased likelihood of advanced LV dysfunction and heart failure compared with thick-filament disease, whereas arrhythmic risk is the same.[34]

## Physical Examination

Examination may be unremarkable or reveal:

- ***Bisferiens pulse*** with dynamic obstruction
- Prominent ***a wave*** in JVP
- ***Systolic murmur*** at left sternal edge. It is distinguished from all other systolic murmurs by an increase in intensity with the Valsalva maneuver and during squatting-to-standing, and by a decrease in intensity during standing-to-squatting action, passive leg elevation, and handgrip.
- ***Pansystolic murmur*** of MR.

## Investigations

**Laboratory tests** Liver and renal function tests, and CK are mandatory. BNP, an independent predictor of survival in HOCM, can identify patients who have poor cardiopulmonary exercise tolerance.[35] Diabetics have a worse prognosis.[36] Other tests are indicated in Table 2.

**Twelve lead ECG** is essential (Table 3) and should be repeated every year once the diagnosis has been established evaluate for asymptomatic changes in conduction or rhythm.

It is abnormal in 75-95% of patients, and may show left atrial enlargement, repolarization abnormalities and inferolateral Q waves. The PR may be short and giant T waves may be present (distal hypertrophy-Japanese variant). QT prolongation (>480 ms) may be seen in 25% of patients.[37]

**Holter monitoring**) is useful to detect paroxysmal AF or non-sustained VT (Table 3). Frequent and prolonged (>10 beats) episodes of NSVT are a marker of sudden death.

**Echocardiography** Transthoracic echo is recommended in the initial evaluation of all patients with suspected HCM (Tables 4 and 5). LV wall thickness > 15 mm in any segment is diagnostic in the absence of other aetiology. In first-degree relatives of patients with unequivocal disease, LV>=13 mm also indicates HCM. Patients with LVOT obstruction >=30 mmHg at rest are at greater risk for heart failure or death in comparison with patients without obstruction.[38] It is considered as an adverse risk factor by the ESC 2014 GL and ,with reservations, by the ESC 2023 GL on cardiomyopathies but not by the AHA/ACC 2020 GL on HCM. LVOT obstruction is usually associated with variable degrees of mitral regurgitation, which when due to SAM is usually directed posteriorly, unless if structural abnormalities of the mitral valve are present. Thickening of the mitral leaflets and anomalous papillary muscle origin may coexist and contribute to obstruction. If the resting instantaneous peak left ventricular outflow tract (LVOT) gradient is ≤50 mm Hg, it is reasonable to perform ***exercise echocardiography*** (not dobutamine stress echocardiography[39]) for detection of exercise-induced dynamic LVOT obstruction (Figure 2). Diastolic dysfunction is frequent and can dominate the clinical presentation to resemble restrictive cardiomyopathy. ***Doppler myocardial strain imaging*** and ***spectrle-tracking echocardiography*** may detect reduced systolic velocity abnormalities, and velocity gradients.[40] ***Transesophageal echocardiography*** is useful if transthoracic echo is inconclusive for clinical decision making about medical therapy and in situations such as exclusion of subaortic membrane, and mitral regurgitation secondary to structural abnormalities of the mitral valve apparatus. It is essential for intraoperative guidance of septal myectomy, and for the intraprocedural guidance of alcohol septal ablation with intracoronary contrast injection of the septal perforator(s).

**Cardiac magnetic resonance** can identify focal hypertrophy as well as hypertrophy, particularly in the anterolateral free wall and apex, that is not well appreciated by two-

dimensional echocardiography (Tables 4 and 6). It is essential in controversial cases.[4, 39] CMR can also provide detailed characterization of other myocardial structures such as the papillary muscles, and enables an accurate assessment of total LV mass and extend of fibrosis. Diffusion tensor cardiovascular magnetic resonance is a novel tool that offers discrimination between HCM and cardiac amyloidosis.[41] Extensive fibrosis assessed by late gadolinium enhancement measured by late gadolinium enhanced CMR seen in 46-60% of patients (increasing with age),[42] and has been reported as a marker of increased risk for sudden cardiac death,[43, 44] although its independent predictive ability regardless of LVEF is not established in all studies.[45] It is considered as an adverse risk factor by the AHA/ACC 2020 GL but not by the ESC 2014 GL. Virtual Native Enhancement is a new deep learning-driven CMR technology that generates images closely resembling conventional LGE without the need for gadolinium- based contrast agent.[46] Apical-basal muscle bundles are a unique myocardial structure commonly detected in HCM by CMR.[47]

**Cardiac CT** may be considered for diagnosis if the echocardiogram is not diagnostic and CMR imaging is unavailable (AHA/ACC 2020 GL on HCM, IIb-C-LD).

**Exercise testing** with simultaneous respiratory gas analysis is useful for demonstration of exercise-induced obstruction, assessment of functional capacity and risk stratification, and for the differential diagnosis of unexplained hypertrophy (Table 7). Up to 25% of patients with HOCM have an abnormal blood pressure response during upright exercise (systolic blood pressure fails to rise > 20–25 mm Hg from baseline or falls), either due to abnormal vasodilatation in non-exercising muscles or impaired cardiac output, and a reduction in peak oxygen consumption compared with healthy controls. Respiratory gas profiles indicative of severe and premature lactic acidaemia can be the only clue to a diagnosis of mitochondrial myopathy.[20] In children with HCM, an abnormal exercise test result was independently associated with lower 5-year transplant-free survival, particularly for patients with an abnormal blood pressure response or exercise-induced ischemia.[48]

**Myocardial perfusion** studies are indicated only in the presence of chest pain or high likelihood of coronary artery disease, not as a routine test for detection of silent coronary disease.

**Invasive haemodynamic assessment** may be required for verification of a dynamic obstruction. Several provocative maneuvers have been used in the catheterization laboratory to identify the presence of a latent gradient, including Valsalva maneuver, inducing a premature ventricular contraction to assess for the Brockenbrough-Braunwald-Morrow sign (post-extrasystolic augmentation in LVOT gradient and reduction in aortic pulse pressure), or upper or lower extremity exercise.[2]

**Coronary angiography** is indicated in the presence of chest pain in patients with a high likelihood of coronary artery disease (Table 8). Angina may also be caused by myocardial

bridging that is common in HCM, [49] or supply/demand mismatch due to the hypertrophy.

**Positron emission tomography** is the most reliable non-invasive quantitative measure of myocardial ischaemia in HCM.[4]

**Programmed ventricular stimulation** has no role in risk stratification (Table 9, see also ICD therapy).

**Endomyocardial biopsy** may be considered when the baseline clinical assessment suggests cardiac inflammation or storage disease which cannot be diagnosed by other means.[50]

Other potentially necessary tests are presented in Table 10. A summary of recommended evaluation and testing in patients with HCM is presented in Figure 3.

## Differential Diagnosis

The likelihood of HCM can be determined by identification of a diagnostic sarcomere mutation or inferred by marked LV thickness >25 mm and/or LVOT obstruction with systolic anterior motion (SAM), and mitral-septal contact. In clinical practice the most commonly encountered conditions that may resemble HCM are essential hypertension and the athletic heart. The **elderly** may also present with sigmoid or hypertophied septum and make diagnosis difficult.[51] Symmetric LV hypertrophy, thickened valves, and moderately depressed LV function in males >65 years old suggest senile or hereditary amyloidosis rather than HCM.[52] Cardiac amyloidosis is often misdiagnosed and difficult to discriminate from HCM. Long-standing **arterial hypertension** produces concentric hypertrophy of the LV but wall thickness >15 mm (>20 mm in blacks) is rare. However, HCM can present with wall thickness <15 mm and, particularly in black patients, diagnosis can be suspected by discovery of a non-hypertensive first degree relative or established by genetic testing. RV hypertrophy and late gadolinium enhancement at the RV insertion points or localized to segments of maximum LV thickening on CMR is indicative of HCM.[53] Regression of LV hypertrophy following 6-12 months of antihypertensive therapy argues against HCM. The **athletic heart** results from intense training. Wall thickness resembling cardiomyopathy may occur in sporting disciplines that combine isometric and isotonic activity, such as cycling and rowing. Sudden cardiac death in young competitive athletes is an important, although rare, public health problem, and a common cardiovascular cause is HCM. Since the phenotypic expression of HCM is variable, and not uncommonly includes patients with mild and localised left ventricular hypertrophy, the differential diagnosis with athlete's heart may be difficult. By contrast with most patients with HCM, athletes have increased left and right ventricular cavity dimensions, normal diastolic function, and rarely have ECG changes suggestive of myocardial disease.[53] Physiological left ventricular hypertrophy can also be differentiated from hypertrophic cardiomyopathy by tissue Doppler imaging velocity measurements.[54] In some cases,

protracted deconditioning may be the only way to establish a diagnosis. Other conditions associated with LV hypertrophy are discussed in "Aetiology" of this Chapter. Differential diagnosis between HCM and and other conditions are presented in Tables 11 and 12.

## Family Counseling and Genetic Testing

Family counselling and genetic testing are essential when the diagnosis of HCM is established (Table 13, Figures 4 and 5). Genetic testing has an important role in the diagnosis and management of HCM in patients and their families, since HCM is inherited as an autosomal dominant trait in most cases, with offspring having a 50% chance of inheriting the same disease-causing genetic variant. Genetic testing should include protein coding and noncoding regions of genes that have established associations with the disease as well as genes that cause diseases that mimic HCM and variants predicted to cause RNA splicing errors.[55] Evaluation of intermediate-effect variant should also be considered when HCM genetic testing is performed.[13] Genetic testing may be useful when metabolic storage disorders with either a very bad prognosis (LAMP2 cardiomyopathy) that indicates heart transplantation or the possibility of therapy (Fabry's disease) are suspected. Postmortem testing for HCM-associated variants
using blood or tissue collected at autopsy is also possible, particularly in instances where the family variant is unknown and no other affected family members are still living.[2]

Despite increasingly large gene panel tests, ~60% of HCM patients remain genotype elusive.[7] Application of genetic testing is relevant whenever one of the known causal genes is responsible for HCM in the family. However, less than 5% of adult patients, but up to 25% of children, with HCM, will have a causative variant in a gene that is known to mimic the HCM phenotype.[1] In addition, the large numbers of pathogenic mutations in different sarcomere protein genes, combined with modifying genetic, epigenetic, and environmental factors, account for why genotype alone cannot predict patient-specific outcomes in HCM.[10] Not all genetic variants in sarcomeric genes cause HCM and many could be benign variants. Finally, absence of a known mutation present in the family does not offer 100% security, since there is possible presence of a second mutation and/or technical errors. Advances in DNA sequencing techniques (deep or massive parallel sequencing) have made genetic screening practical with a diagnostic yield of approximately 50% with familial HCM, but lower (<30%) when sporadic disease is considered (see www.genetests.org).

In genotype-negative relatives of individuals with genotype-positive HCM, no further clinical follow-up is required.[2] The majority of child carriers of sarcomere gene mutations and child relatives with unknown genetic status do not develop HCM, at least within the next 12 years of follow-up.[6]

## Risk stratification

Younger age at diagnosis and the presence of a sarcomere mutation are strong predictors of adverse events.[32] HCM is a common cause of sudden death in young people (<=1% annually and predominantly in patients<25 years), including competitive athletes.[56] However, the incidence of SCD in the general population 10 to 45 years of age is an order of magnitude lower than previously reported, and infrequently related to exercise.[57] Sudden death is paradoxically low in patients >60 years of age.[31] It is caused by fast VT or VF due to reentry in the electrophysiological substrate of scarring and disarray. There is no evidence that bradyarrhythmias play a role. In patients with HCM, SCD risk stratification should be performed at the time of initial evaluation and periodically thereafter.[58]

High risk factors are (Table 14):

**Previous cardiac arrest (although most are lethal)**

**Unexplained syncope**

**Massive LV hypertrophy (>=30 mm)**

**Family history of HCM-related sudden cardiac death**

**Non-sustained VT on Holter**

A sudden cardiac death risk prediction model (**HCM Risk-SCD** formula) that provides individualized risk estimates has been developed.[59] It considers age, maximal left ventricular wall thickness, left atrial diameter, left ventricular outflow tract gradient, family history of SCD, non-sustained ventricular tachycardia, and unexplained syncope. It has been adopted by the ESC 2014 GL on HCM, and its ability to improve the risk stratification of patients with HCM for primary prevention of SCD has been verified.[60] It is available online at http://www. doc2do.com/hcm/webHCM.html. In children, the ESC recommends the use of the **HCM Risk-Kids** tool (https://primacy.shinyapps.io/calculator/).[1]

Risk factors of poor prognosis for patients with HCM with **left ventricular systolic dysfunction** are multiple pathogenic/likely pathogenic sarcomeric variants, AF, and LVEF <35%.[25] Patients with **LV apical aneurysms** are at high risk for arrhythmic sudden death and thromboembolic events.[61] **Sustained VT** has a similar prognostic impact to SCD, although it is relatively uncommon in HCM, and raises suspicion of a left ventricular apical aneurysm.[62] Abnormal exercise blood pressure response may be associated with a higher risk of SCD in adult patients aged ≤40 years, but it has a low positive predictive accuracy and its prognostic significance in patients >40 years of age is unknown.[1] The presence of **end-stage disease** with widespread LV scarring and delayed gadolinium enhancement in MRI are probably additional important risk factors. Three of the five principal risk predictors (NSVTVT, abnormal blood pressure response to exercise, and marked LV hypertrophy) have significantly higher predictive potential in young adult HCM patients than the >50 age group,

and a family history of SCD is also considered less relevant with advancing years.[62] Asymptomatic patients with none of these factors are at low risk (<0.5%/year), although risk factors are not identified in 3% of SCD victims.[62 63] Patients with diabetes have a worse outcome with more heart failure symptoms and increased mortality.[36]

**Sarcomeric** HCM is associated with worse prognosis and may benefit from more vigilant surveillance for arrhythmias and systolic dysfunction.[64] Cardiovascular comorbidities (ie, hypertension and obesity) are more prevalent in patients with **nonsarcomeric** HCM, suggesting a potential causal link with disease development.[64] **LAMP2 cardiomyopathy** is largely refractory to ICD therapy and has a poor prognosis.[65] The potential association of double, triple or **compound sarcomere mutations** (5% of patients with HCM) with a higher risk has also been under consideration.[66, 67] Patients with pathogenic variants in genes encoding proteins that interact within the RAS/mitogen-activated protein kinase pathway (RASopathy) and HCM also face higher risks of nonarrhythmic death or progression to cardiac transplantation.[68]

The majority of surviving adults who had **HCM diagnosed in childhood** have no symptoms. In children, HCM peak incidence is during the first year of life. The greatest risk of death or transplantation is in the first year after diagnosis (14%).[69]

## Therapy

The management of patients with HOCM is aimed at restricting extreme activity with avoidance of volume depletion, symptomatic relief, prevention of sudden death, and screening of relatives. With the exception of ICD, no pharmacological or other strategies offer protection from sudden death. Contemporary therapeutic interventions including ICD, have resulted in a ow disease-related mortality of 0.5-1%/year.[70 4]

**Medical therapy**

In asymptomatic HCM patients, benefit from beta-blockers or L-type calcium channel blockers has not been established, but beta-blockers are first-line agents for the management of symptomatic (angina or dyspnea) patients with HCM (Table 15, Figures 6 and 7).

***Beta blockers***, particularly without intrinsic sympathomimetic activity and aimed at heart rate <60-65 bpm, improve ventricular relaxation, increase diastolic filling time, and should theoretically reduce susceptibility to ventricular arrhythmias. They are the mainstay of treatment for symptomatic improvement.[71]

***L-type calcium channel blockers*** such as ***verapamil*** (starting in low doses and titrating up to 480 mg/d) and ***diltiazem*** are beneficial due to negative inotropic and chronotropic effects and improved diastolic function and are used instead of or with beta blockers. They may,

however, exacerbate LVOT gradient due to vasodilation. They are particularly useful in the nonobstructive form.

The ***myosin inhibitors mavacamten*** and ***aficamten*** are well tolerated and associated with reduction in of LVOT obstruction and NYHA functional class.[72-74] In the ODYSSEY-HCM RCT, mavacamten did not result in a significantly greater improvement in peak oxygen uptake or decrease in symptoms than placebo,[75] but in the SCOUT-HCM RCT among adolescent patients with obstructive hypertrophic cardiomyopathy, the reduction in left ventricular outflow tract obstruction was significantly greater with mavacamten than with placebo over a 28-week period.[76] In the MAPLE-HCM RCT, aficamten monotherapy was superior to metoprolol monotherapy in improving peak oxygen uptake and hemodynamics and decreasing symptoms,[77] and in the ACACIA-HCM RCT aficamten was associated with improvements across a broad range of clinically relevant measures including symptom burden and diastolic function.[78, 79]

***Disopyramide*** in combination with beta blockes reduces LVOT gradient and improves symptoms by its negative inotropic action. Although it has not been considered proarrhythmic in HCM,[80] concerns about the inherent proarrhythmia of Class IA agents cannot be ignored. Significant vagolytic side effects such as dry mouth and prostatism occur in 5% of patients.

***Vasodilators***, including dihydropyridine calcium channel blockers and angiotensin-converting enzyme inhibitors, are potentially harmful in those with evidence of LVOT obstruction.

***Amiodarone*** is not considered a therapeutic option for prevention of sudden death in HCM any more.

Specific therapy is needed for conditions resulting in ventricular hypertrophy, such as enzyme replacement therapy in ***Fabry disease*** (alpha-galactosidase A deficiency), or ***amyloidosis***.[50]

**Septal Reduction**

***Septal myectomy*** is considered for patients with significant LVOT gradients, ≥30 mm Hg at rest or ≥50 mm Hg during exercise, and symptoms refractory to medical therapy (Table 16 and Figure 8).[81] Operative mortality in experienced centers is < 1.5%, and the risk of VSD 1% and of complete heart block 6%.[81, 82] However, in a recent survey in Dutch hospitals, thirty-day complication rates concerned mortality (5%), ventricular septal defect (2%), stroke (3%), and surgical reoperation (2%).[83] Mitral abnormalities play a particularly important role in patients with mild or moderate hypertrophy. Patients with mitral abnormalities should be treated by septal reduction alone in association with surgical mitral valve repair or replacement.[84] In the absence of intrinsic MV disease, the MR is relieved by myectomy alone.[85] Cutting thickened and/or retracted secondary chordae of the anterior mitral leaflet in association with septal myectomy has been reported to result in favorable long-term clinical and hemodynamic results in patients with obstructive HCM, with an intra-operative mortality of 0.6%.[86]

***Transcatheter septal ablation*** with, usually, alcohol infusion can be considered in symptomatic patients with accessible septal branch and septal thickness ≥15 mm, significant LVOT gradient, ≥30 mm Hg at rest or ≥50 mm Hg on provocation, and absence of intrinsic abnormality of the mitral valve and of proximal left anterior descending coronary artery stenosis.[87, 88] Other methods such as radiofrequency or electrosurgical myotomy are also available.[89-91] Septal ablation has uncertain effectiveness with marked septal hypertrophy (>30 mm). Mortality is <3%, and the risk of permanent pacemaker 10-30% but it is reduced with contrast echocardiography and slow ethanol injection.[92] On the basis of CMR and necropsy studies, septal ablation is associated with scarring not seen in myectomy.[93] There is an incompletely defined risk of ventricular arrhythmias arising at the borders of the iatrogenic scar,[3] and this option is not recommended in young patients. In non-randomized comparisons, up to 5-year survival offered by septal ablation was similar to that of an age- and sex-matched general population, and to patients undergoing surgical myectomy, as well, without an increased risk of sudden cardiac death. [94-97] Septal myectomy is associated with higher risk of short-term mortality and complications compared with alcohol ablation, but with lower risk of mortality in the long term.[98, 99]

No mortality benefit has been detected with either transcatheter or surgical septal reduction compared to medical therapy,[87] and in patients with preexisting risk factors for sudden death an ICD should be implanted before septal ablation. In addition, despite initial clinical benefit after relief of obstruction, 13% of patients develop heart failure o ratrial fibrillation over long-term follow-up because of the cardiomyopathic process.[100]

**Pacing**

***DDD pacing*** with a short AV delay has been shown to decrease LVOT gradient and symptoms in some but not all randomized comparisons.[101, 102] It may be useful in the elderly without short PR intervals (Table 17), and in medically refractory symptomatic patients with LVOT obstruction who are suboptimal candidates for septal reduction therapy. Antitachycardia pacing for VT may be useful.[28]

**ICD**

Although no randomized studies exist in HCM populations (as in ischemic cardiomyopathy), there is consensus that in high risk patients defined as those with a history of cardiac arrest or with >=2 risk factors, ICD are indicated (Table 18, Figures 9 and 10). According to the HCM Risk-SCD model that has been adopted by the ESC, patients with a 5-year sudden cardiac death risk ≥6% should be offered an ICD, whereas patients with a 5-year sudden cardiac death risk ≤4% should be regularly reassessed.[60] Potential complications of ICD therapy are pneumothorax, haematoma, lead revisions, and infection. The main concern, however, is inappropriate shocks that may occur in up to 36% of patients with a rate of 5% per year.[103] Extreme LV hypertrophy is the most common risk factor in children and an ICD when

indicated can be life-saving. However, the complication rate (inappropriate shocks and lead malfunction) may be up to 3-fold higher that interventions for VT/VF.[104]

Primary prevention ICDs are implanted more frequently in patients with HCM in US vs. non-US sites (Europe, Australia and Brazil) across the spectrum of SCD risk. There was a lower rate of appropriate ICD therapy in US sites, consistent with a lower-risk population, and no significant difference in SCD in US vs. non-US patients who did not receive an ICD.[105]

**Atrial fibrillation**

AF occurs in 20% of patients with HCM (4-fold than in the general population).[38] It can cause sudden and sometimes severe deterioration in symptoms and exercise capacity, and is associated with a high risk of thromboembolism. Restoration of sinus rhythm usually results in a substantial improvement in symptoms, and amiodarone may be effective in preventing recurrences,[106] but its long-term use is limited by its side-effects. Control of the ventricular rate with b blockers, calcium antagonists, or both is almost as effective. Because of the potentially adverse effects of digoxin in patients with hypertrophic cardiomyopathy and normal systolic function, this drug is not routinely recommended for rate control. All patients with permanent or paroxysmal AF in the context of an enlarged atrium should be anticoagulated (Table 19). Catheter ablation may offer restoration of sinus rhythm and improvement of symptomatic status in up to 50% of patients (see Chapter on AF).[107]

**Ventricular arrhythmias**

Beta blockers are the first treatment option. Other antiarrhythmic drugs are used to reduce ICD shocks (Table 20), In general, they have no impact on mortality, and there is a potential for increased mortality with amiodarone (see Chapter on VT).

**LV dysfunction and heart failure**

Recommendations are provided in Table 21 and Figures 11 and 12. Heart transplantation is the last option for patients with irreversible heart failure due to systolic dysfunction.

**Other comorbidities**

The management of other comorbidities is presented in Table 22.

**New therapies**

The cardiac mitotrope ***ninerafaxstat*** shifts cardiac energy metabolism from free fatty acid oxidation to glucose oxidation, reducing the amount of oxygen required per mole of ATP generated, and thereby increasing cardiac efficiency. Preliminary experience has been promising.[108] In patients with fibrotic and retracted MV chordae, trans-aortic chordal cutting may also be useful, but experience is limited.[109] Therapies targeting the genome also appear. There is intense interest in the potential of therapies targeting the underlying genetic defect in cardiomyopathies, including gene repair mechanisms via CRISPR/cas9, splicing correction, gene replacement, and RNA interfering methods leading to gene silencing.[7]

## Physical Activity and Sports

In patients with hypertrophic cardiomyopathy without left ventricular outflow tract obstruction, supervised exercise training improves both functional capacity and cardiac function.[110] Thus, patients are allowed to participate in low-intensity sports. Intensive competitive sports should be avoided in high-risk individuals (Table 23).[111-113] However, the optimum exercise prescription remains to be determined, since the marked benefits of regular exercise may outweigh the risks of inactivity,[114] and exercise guidelines in hypertrophic cardiomyopathy may be too restrictive.[57] Cardiac arrest is rare in patients with HCM and emerging data is shifting towards support for the safety of exercise in this patient population.[115] For sports classification see also Chapter on Athletes. Occupational issues are presented in Table 24.

## Noncardiac Surgery

Recommendations are provided in Table 25.

## Follow-up

Recommendations are provided in Table 26 as well as in the discussion of Investigations.

## Pregnancy

It is not contraindicated either in no-obstructive or obstructive HCM. Serious complications are rare (1-2%); caution is needed in patients with significant gradient when administering epidural anesthesia that induces peripheral vasodilation (Table 27).[116-118]

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