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Primer

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Hypertrophic cardiomyopathy

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Abstract

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiomyopathy and represents a leading cause of morbidity and mortality. HCM is a sarcomeric disease characterized by genetically determined defects in sarcomere proteins, leading to left ventricular hypertrophy, hypercontractility and diastolic dysfunction. The phenotypic spectrum of the disease is heterogeneous, ranging from mild forms that can remain stable and asymptomatic for many years, through to childhood-onset, severe cases that can result in progressive heart failure and ventricular arrhythmias. Multi-imaging techniques including echocardiography and cardiac magnetic resonance are pivotal for diagnostic and prognostic assessment in HCM. For decades, therapeutic approaches were limited to invasive septal reduction therapies and nonspecific pharmacological treatment for heart failure. In the last 10 years, however, an in-depth understanding of the pathological mechanisms of HCM has led to the development of targeted therapies, such as myosin inhibitors, which have proven to be safe and effective in improving functional capacity and reducing symptoms. Innovative therapeutic approaches, such as gene therapies that aim to target the genetic variants underpinning the condition, are currently under investigation.

Sections

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Introduction

Hypertrophic cardiomyopathy (HCM) is a heart disease characterized by increased left ventricular wall thickness in the absence of abnormal loading conditions, such as hypertension or aortic stenosis[1]. Mechanistically, HCM is most commonly associated with variants in genes encoding sarcomere proteins that facilitate cardiac muscle contractility (known as sarcomeric HCM). So far, variants in 25 genes have been demonstrated conclusively or with strong evidence to be causative of HCM, and a further four genes have moderate evidence of causation[2]. Various other aetiologies of HCM, collectively defined as HCM phenocopies, have been described, including lysosomal disorders (such as Danon disease and Fabry disease), diseases of the RAS–MAP kinase pathway (such as RASopathies), mitochondrial diseases, Friedreich ataxia and cardiac amyloidosis. When HCM results in left ventricular outflow tract obstruction (LVOTO), it is defined as 'obstructive' HCM (Fig. 1), otherwise, the phenotype is described as 'non-obstructive'.

The estimated prevalence of HCM is at least 1 in 500 adults (0.5%) worldwide[1]. HCM is a leading cause of morbidity and mortality in young patients with cardiomyopathy, with 60% of patients that are diagnosed with HCM before 40 years of age having at least one heart failure-related event by the age of 70 years[3]. Ventricular arrhythmias and sudden cardiac death (SCD) are the most dreaded complications; however, the overall risk of these complications is lower than previously thought, particularly past middle age[3]. However, HCM can be associated with several serious symptoms including dyspnoea (shortness of breath) on exertion, angina (chest pain or pressure), asthenia (weakness) and syncope (fainting). The standard therapeutic armamentarium includes β-blockers, calcium channel blockers and antiarrhythmic drugs and, in selected cases, the implantation of an implantable cardiac defibrillator[4]. Improvements in our understanding of the pathological mechanisms of HCM, accrued over the past five decades, have led to the development of innovative therapeutic approaches, such as cardiac myosin inhibitors and gene therapies, which hold the promise of changing the natural history of the disease.

In this Primer, we provide an overview of the epidemiology of HCM, its pathogenetic mechanisms, diagnostic steps and established treatments for HCM. We also discuss the effect of HCM on the quality of life of patients, and we conclude by highlighting areas for further research and novel treatments under development.

Epidemiology

Estimating the true prevalence of HCM remains challenging due to the intrinsic heterogeneity of the disease. Prevalence studies using echocardiography have estimated a worldwide prevalence of left ventricular hypertrophy (wall thickness ≥15 mm) of 1 in 500 people (0.2%), corresponding to approximately 15 million individuals[5]. Cardiac magnetic resonance (CMR) has a higher sensitivity for detecting left ventricular hypertrophy, and, using this technique in a cohort of patients between 45 and 84 years old, the prevalence was reported to be as high as 1 in 74 people (1.35%)[6]. Data from health record databases in the USA from 2019 showed an estimated prevalence of clinically diagnosed HCM of 0.07% (ref. 7), whereas in the UK Biobank, the prevalence of pathogenic sarcomeric variants associated with HCM (*MYBPC3*, *MYH7*, *MYL2*, *MYL3*, *TNNI3*, *TNNT2*, *TPM1* and *ACTC1* genes) was 0.25% (ref. 8). However, the condition probably remains underdiagnosed, given that patients can be paucisymptomatic, echocardiographic findings can be subtle and screening programmes are lacking[5].

Women are frequently under-represented in prevalence studies of the HCM population, accounting for only 30–45% of HCM cases, a phenomenon that has remained unchanged over the last three decades[9]. A likely explanation is that women are underdiagnosed, with women presenting at a more advanced disease stage, being older at diagnosis and having a worse survival compared with men[10]. Despite women having smaller left ventricular dimensions compared with men, a sex-specific threshold for HCM diagnosis is lacking, which may further contribute to missed or delayed diagnosis in women[10].

Differences in clinical presentation, management and outcomes have been identified across ethnicities in people with HCM. African American patients, although presenting similar clinical characteristics compared with white patients[11], had a higher burden of symptomatic heart failure, were less likely to undergo invasive septal reduction therapies despite similar degrees of obstruction and less frequently underwent genetic testing[12]. Asian patients are often older at diagnosis, are more likely to present with apical hypertrophy (involving the apex of the left ventricle) and have a lower prevalence of LVOTO compared with Europeans[13]. Genetic testing is seldom performed in Asia compared with Europe (2% versus 17% of patients), probably reflecting lack of financial reimbursement to patients by the national health system. Furthermore, Asian patients with HCM have a higher risk of mortality, hospitalization for heart failure and implantable

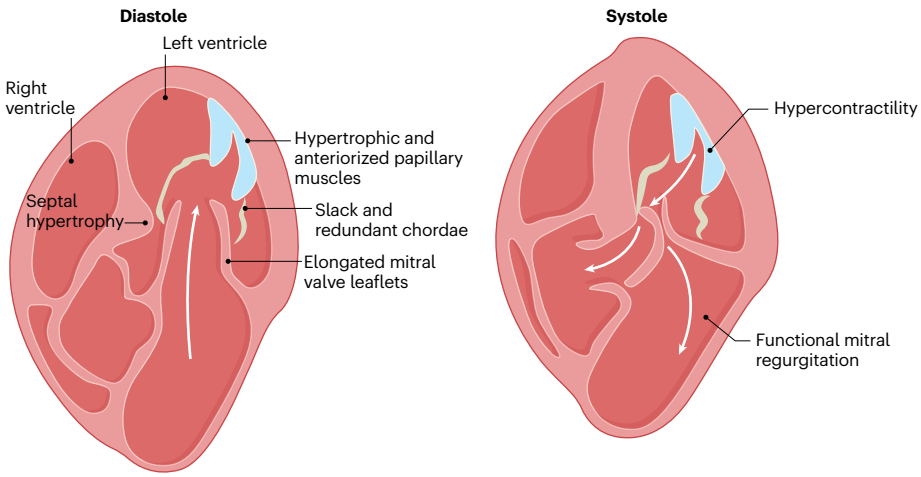

Fig. 1 | Left ventricular outflow tract obstruction. Left ventricular outflow tract obstruction is caused by hypertrophic and anteriorized papillary muscles that, together with slack and redundant chordae, move the mitral leaflet coaptation point (the point at which the leaflets of the valve come into contact during closure) towards the left ventricular outflow tract. As a result, the elongated mitral leaflets, under increased force due to hypercontractility, touch the hypertrophied septum, thereby hindering the blood from flowing into the aorta during systole. Some blood can flow back into the left atrium, resulting in functional mitral regurgitation.

cardioverter–defibrillator (ICD) shocks, compared with Europeans[13]. These differences are probably influenced not only by ethnicity but also by sociocultural factors, as well as access to care and care patterns, all of which should be urgently addressed.

The true prevalence of HCM in children is unknown, but is estimated to be in the region of 3 cases per 100,000 children[14], and epidemiological studies from Australia[15], North America[16] and Finland[14] have suggested an annual incidence of between 0.24 and 0.47 cases per 100,000 children. These figures are likely to be an underestimate of the true incidence and prevalence, largely reflecting data from an era before routine availability of genetic testing and multimodality imaging.

Mechanisms/pathophysiology

Pathophysiology

The pathophysiology of HCM has historically been described in terms of the direct haemodynamic consequences of LVOTO and myocardial hypertrophy[17], observed initially as a 'tumour' of the left ventricle[18]. As genetic sequencing technologies became routine in academic research, families with HCM driven by disease-causing genetic variants in crucial sarcomere genes were increasingly reported[19,20]. These observations ultimately led to a shift in understanding of the underlying pathophysiology of HCM from a hypertrophic tumour-like overgrowth to the disease being a hypertrophic response of the cardiac muscle to hypercontractility caused by inborn errors in the sarcomere.

The sarcomere, hypercontractility and hypertrophy. The sarcomere is the molecular motor of the cardiomyocyte, contracting in response to calcium-induced calcium release triggered during the plateau phase of the myocyte action potential. Calcium released from the sarcoplasmic reticulum leads to retraction of tropomyosin away from the actin scaffold, allowing binding of the myosin head, conversion of ATP to ADP + Pi and myosin heads to pull the edges of the sarcomere together along the actin scaffold. Myosin heads bound to actin have an elevated rate of ATPase activity, defined as actin-activated activity (fast), whereas myosin heads when not interacting with actin can be in either the disordered relaxed (DRX) state (100× slower ATPase activity than actin-activated state) or the super-relaxed (SRX) state (10× slower than DRX state). The basal ATPase activity of myosin is represented by the DRX state, with myosin heads available for interaction with actin, whereas, the SRX state conserves energy in relaxed muscle[21].

HCM genetic variants cause increased contractility by several mechanisms. Missense, gain of function variants in the converter domain of the myosin heavy chain 7 (*MYH7*) increase the number of myosin heads in the DRX state, thus increasing the availability of myosin molecules ready to engage actin per sarcomere unit[22]. Truncating and non-truncating variants localized in the C10 domain of *MYBPC3* lead to myosin binding protein C (MYBPC) haploinsufficiency, destabilization of the SRX population and increase in myofilament sliding velocity, whereas C3 and C6 variant MYBPC are incorporated normally and their impact on contractile function has not yet been fully elucidated[23,24]. Variants in thin filaments genes (comprising actin, troponin complex and tropomyosin) increase the sensitivity of the sarcomere to calcium, leading to enhanced contractility in response to less calcium-induced calcium release and severe diastolic dysfunction[25,26]. Changes in sarcomere protein structure and function are thought to cause downstream activation of signalling pathways, such as TGFβ signalling, that promote myocyte fibril disarray and left ventricular hypertrophy, although these mechanisms remain incompletely understood[27]. The hypercontractile state characterizing HCM is responsible for major downstream consequences such as development of LVOTO, diastolic dysfunction and energy profligation, ultimately resulting in various degrees of tissue damage and replacement fibrosis (Fig. 2).

Microvascular dysfunction and fibrosis. Structural and functional abnormalities of the microcirculation are associated with the development of ischaemia without obstructive coronary artery disease, fibrotic remodelling and ventricular arrhythmias. The presence of cardiac small vessels with thickened walls and a reduced density is a hallmark of HCM histology[28]. Furthermore, hypercontractility and impaired relaxation cause excessive microcirculatory compression in systole and impaired decompression in diastole, which lead to reduced coronary vasodilator reserve (the capacity of the coronary arteries to dilate)[29]. Abrupt increases in energetic demands, such as during exercise or stress, can trigger ventricular arrhythmias, whereas chronic ischaemia can cause myocyte death and replacement fibrosis, eventually causing left ventricular wall thinning and systolic dysfunction. Besides replacement fibrosis, an expansion of the extracellular matrix (interstitial fibrosis) can be promoted by the increased TGFβ signalling associated with pathogenic sarcomeric variants[28]. The presence of surviving myocardial bundles separated by insulating layers of collagen may create re-entry circuits and favour the development of ventricular arrhythmias. Thus, the presence of extensive fibrosis (>15% of left ventricular mass) has been associated with an increased risk of SCD[4].

Metabolic derangements in HCM. Because HCM is caused by sarcomeric variants that result in increased force generation, it leads to substantial metabolic demands and reliance on mitochondrial function to sustain energy output. A consequence of such heighted metabolic activity is impaired release and reuptake of calcium (calcium cycling), increased intracellular ADP levels and, consequently, dysfunction of the mitochondrial electron transport chain, all of which probably contribute to myocardial stiffness (diastolic dysfunction), fibrosis burden and arrhythmia. Comprehensive multiomic profiling of HCM energetics from myocardial tissue revealed alterations in fatty acid metabolism, acylcarnitines depletion and free fatty acid accumulation[30]. These metabolic changes were coupled with evidence of energetic failure highlighted by a reduction in high energy phosphate metabolites (such as ADP) and electron microscopic evidence of mitochondrial disarray and degradation without upregulation of expected mitophagy clearance[30]. Data from myectomy samples showed reduced capacity for oxidative phosphorylation and fatty acid oxidation in patients irrespective of whether they had confirmed sarcomere variants[31]. In patients without sarcomere variants, mitochondrial dysfunction parameters were strongly associated with left ventricular hypertrophy, probably having an important role in hypertrophic remodelling similarly to mitochondrial cardiomyopathies[31].

Ion channel involvement. HCM arrhythmic propensity might be partially explained by the presence of an acquired channelopathy. Sarcomeric variants may promote hyperactivation of Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), leading to post-translational modifications of ion channels[32]. Indeed, HCM cardiomyocytes show a prolonged action potential duration due to an increased late sodium current (INaL), and L-type calcium channel (ICaL) amplitude, slower ICaL inactivation and decreased potassium currents[33]. Action potential duration prolongation augments the probability of early afterdepolarizations, whereas calcium overload can lead to enhanced spontaneous Ca-release from the sarcoplasmic

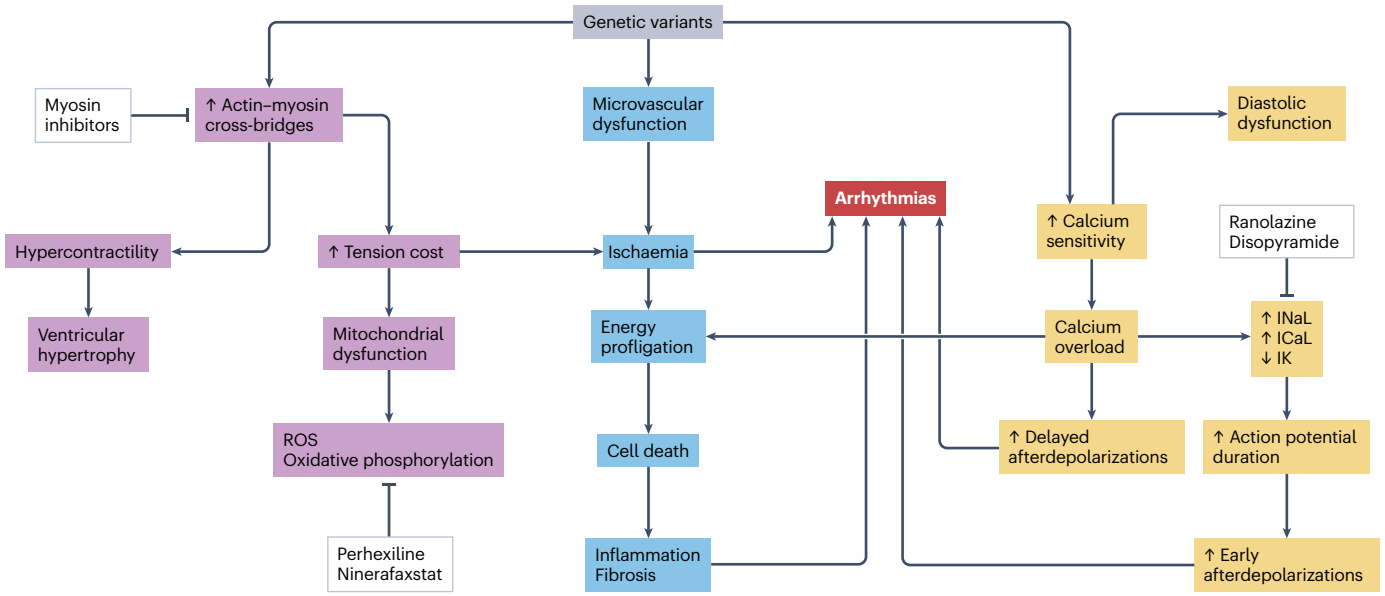

Fig. 2 | Pathophysiology of hypertrophic cardiomyopathy. The presence of a pathogenic genetic variant in genes encoding components of the sarcomere can have several deleterious consequences. Left, the purple boxes indicate that an increased number of actin–myosin cross bridges can drive hypercontractility and energetic impairment. Centre, the blue boxes indicate that microvascular abnormalities and dysfunction can result in ischaemia, necrosis, inflammation and fibrosis, contributing to arrhythmias (red box). Right, the yellow boxes indicate that increased calcium sensitivity can promote diastolic dysfunction and arrhythmias. Drugs targeting the different pathogenic steps of hypertrophic cardiomyopathy are shown in white boxes. ICaL; L-type calcium current; IK, potassium current; INaL, late sodium current; ROS, reactive oxygen species.

reticulum and delayed afterdepolarizations, overall resulting in a proarrhythmic profile.

LVOTO. LVOTO is perhaps the most well recognized feature of HCM pathophysiology and is caused by hypercontractility in conjunction with several left ventricular anatomical abnormalities. LVOTO can be found in patients with HCM, either at rest or after provocative measures such as the Valsalva manoeuver (forceful exhalation against a closed airway), administration of nitrates or exercise[34]. Obstructive HCM is defined by an outflow gradient that is higher than 30 mmHg, with a gradient of ≥50 mmHg being considered haemodynamically relevant, warranting specific therapies[4]. LVOTO occurs during ventricular systole when hypercontractility combined with hypertrophy generates drag forces that push the mitral leaflets towards the LV septum, hindering blood outflow. An increase in blood velocity when passing through the constricted outflow tract is also thought to occur (known as Venturi force), although this occurs in the terminal phase of systole. Obstruction is exacerbated by anatomical abnormalities in the mitral apparatus, including elongated mitral valve leaflets, anteriorized and hypertrophic papillary muscles, and long and lax chordae that force the coaptation point of the mitral valve anteriorly, possibly leading to functional mitral regurgitation[35]. LVOT obstruction can also develop in patients with progressive angulation of the outflow tract even in the absence of substantial septal hypertrophy (septal thickness <15 mm)[36,37]. The obstruction is typically dynamic and can be relieved by increased left ventricular volume load ('stenting' open the outflow tract) but is worsened by increased contractility (such as from increased myocardial calcium load after a premature ventricular contraction, as is observed in the Brockenbrough–Braunwald–Morrow effect) and hypovolaemia (such as due to dehydration or postprandial gastrointestinal hyperaemia).

Molecular aetiology

HCM is widely regarded as a disease of the sarcomere. There are currently nine genes encoding for sarcomere proteins with strong evidence of causation for HCM: *MYBPC3*, *MYH7*, *TNNT2*, *TNNI3*, *TNNC1*, *TPM1*, *ACTC1*, *MYL2* and *MYL3* (Table 1). Of those, variants in *MYBPC3* and *MYH7* are by far the most prevalent in HCM populations worldwide. Additional HCM-associated genes that have recently been classified as having definitive or strong evidence include *FLNC*, *ALPK3*, *PLN*, *CSRP3* and *ACTN2*, whereas *JPH2*, *TRIM63* and *KLHL24* are classified as having moderate evidence of disease association (Fig. 3 and Table 1). These classifications are based on guidelines published by the American College of Medical Genetics and the Association of Molecular Pathology in 2015, which provide a framework for sequence variant interpretation in Mendelian disorders[38]. The variant classifications include 'pathogenic' (P), 'likely pathogenic' (LP), 'variant of uncertain significance' (VUS), 'likely benign' (LB) and 'benign' (B). The list of causative genes in HCM continues to expand as more evidence is collated from clinical and research groups worldwide. However, a rare causal variant is identified in around 30–60% of cases, suggesting the presence of unidentified causal genes and potentially polygenic, non-Mendelian aetiologies of HCM[39]. Population studies showed the incomplete penetrance and variable expressivity of rare variants[8], and both low penetrance sarcomere variants and common variants might contribute to HCM pathogenesis, highlighting the complex genetic architecture of this condition[40,41]. Further research is needed to improve our understanding of the genetic background of the disease and its correlation with disease expression.

Diagnosis, screening and prevention

Natural history of HCM

HCM is highly variable in its clinical expression, ranging from asymptomatic individuals to those severe phenotypes at risk of SCD. Below, we describe the natural history of HCM, from presymptom stage through to overt cardiac dysfunction.

Stage 1 pre-phenotype expression and HCM development. Individuals that carry HCM-associated genetic variants can be identified by cascade genetic screening in affected families. These individuals are by definition free from symptoms and overt HCM manifestations, including left ventricular hypertrophy. Nevertheless, they may present subtle abnormalities reflecting their genetic predisposition, including myocardial crypts, histological features such as cardiomyocyte disarray[42], microvascular remodelling and perfusion defects[43], a smaller left ventricular cavity, elongation of the mitral valve leaflets, a hypercontractile function and electrocardiogram (ECG) alterations[43–45]. These abnormalities may be present before the development of a full-fledged form of HCM[46]. Excluding some neonatal HCM forms in which infants harbour biallelic mutations[47], left ventricular hypertrophy usually appears in adolescence or early adult life[48], although its onset can occur as late as the sixth or seventh decade[49]. The penetrance in patients with pathogenic or likely pathogenic variants identified during cascade screening is ~60% (ref. 50), with male sex and abnormal ECG associated with a higher risk of developing HCM in disease-causing variant carriers[51].

Stage 2 overt HCM phenotype. In the early phases of HCM, when most patients are diagnosed, the hypertrophic, hypercontractile phenotype is fully expressed, but there is little or no evidence of fibrotic changes. At this stage, the most common cause of symptoms is LVOTO, and patients may complain of dyspnoea on exertion, angina and syncope, accentuated in the postprandial state. Patients with non-obstructive HCM may present with dyspnoea and angina related to microvascular ischaemia and diastolic dysfunction[52]. On average, patients with pathogenic or likely pathogenic variants show the greatest propensity for development of heart failure-related complications, compared with those with VUS and genotype-negative patients, in this order[3].

Stage 3 adverse remodelling. Up to 15% of patients may progress from the 'classic' HCM phenotype (hypertrophy and hypercontractility) to a stage dominated by maladaptive changes heralding disease progression and worsening left ventricular function due to extensive fibrosis. A decline in left ventricular systolic function in the 50–60% range (from an average exceeding 70% in the classic form) should be regarded with high suspicion, particularly when associated with spontaneous loss of LVOTO and the presence of late gadolinium enhancement >15% in the left ventricle on cardiac magnetic resonance imaging (MRI), as this stage may predict progression to heart failure[53]. Notably, despite substantial left ventricular remodelling, patients can experience only mild symptoms, such as dyspnoea upon moderate exertion. However, atrial remodelling is often severe and the onset of atrial fibrillation is common. Atrial fibrillation is associated with high risk of thromboembolic complications, mandating oral anticoagulation[4]. When left atrium dilatation and dysfunction are severe, patients can incur ischaemic stroke even in the absence of atrial fibrillation[54].

Stage 4 overt dysfunction. Overt left ventricular systolic dysfunction (LVSD, ejection fraction <50%) or left ventricular restriction develops in <10% of patients with HCM and represents a challenging condition often associated with refractory heart failure. In a large cohort with LVSD, 75% of patients developed heart failure-related events and 53% met a composite outcome including all-cause death, cardiac transplantation or left ventricular assist device implantation after a median follow-up of 8 years[53]. Thus, it is extremely important to identify patients with LVSD and refer them for transplant evaluation in a timely manner, as prohibitive pulmonary pressures may develop rapidly, even at a young age, and the severity of this condition might be overlooked in the presence of falsely reassuring left ventricular ejection fraction (LVEF) values (~50–60%). Predictors of incident HCM-induced LVSD include greater left ventricular cavity size, LVEF between 50% and 60%, fibrosis on cardiac MRI and the presence of pathogenic or likely pathogenic genetic variants, particularly in thin filament genes[53]. Patients harbouring variants in genes encoding thin filament proteins (such as *TNNI3*, *TNNT2*, *ACTC1*, *TPM1* and *TNNC1*) present with milder and circumferential left ventricular hypertrophy (concentric hypertrophy) or involving the apical area (apical hypertrophy). They show a more frequent progression to advanced heart failure symptoms and a have a higher risk of developing severe diastolic dysfunction and overt systolic dysfunction (ejection fraction <50%), particularly in children[55].

Definition and diagnostic criteria

In adults, HCM is diagnosed by the finding of an otherwise unexplained left ventricular wall thickness ≥15 mm in at least one myocardial segment. The diagnosis can also be established with less severe wall thickening (13–14 mm) if other features are present, including family history of HCM (evaluated by collecting a three-generation family history), specific genetic findings and ECG abnormalities[4]. The most commonly accepted threshold for the diagnosis of HCM in children is a maximal left ventricular wall thickness of >2 standard deviations above the predicted body surface area-corrected mean (*z*-score >2)[4].

Table 1 | Genetic causes of HCM

Gene symbol	Gene name	Inheritance pattern	Frequency of disease
MYBPC3	Myosin binding protein C3	AD, AR	40–45%
MYH7	Myosin heavy chain 7	AD	15–25%
TNNT2	Troponin T, type 2	AD	1–7%
TNNI3	Troponin I, type 3	AD	1–7%
TPM1	Tropomyosin 1	AD	1–2%
ACTC1	Actin α-cardiac muscle 1	AD	1–2%
MYL2	Myosin light chain 2	AD	1–2%
MYL3	Myosin light chain 3	AD, AR	1–2%
FLNC	Filamin C	AD	<1%
PLN	Phospholamban	AD	<1%
ALPK3	α-Kinase 3	AR	<1%
CSRP3	Cysteine and glycine rich protein 3	AD	<1%
TNNC1	Troponin C, type 1	AD	<1%
FHOD3	Formin homology 2 domain containing 3	AD	<1%
ACTN2	α-Actinin 2	AD	<1%
CACNA1C	Calcium voltage-gated channel subunit-α1C	AD	1%

AD, autosomal dominant; AR, autosomal recessive; HCM, hypertrophic cardiomyopathy.

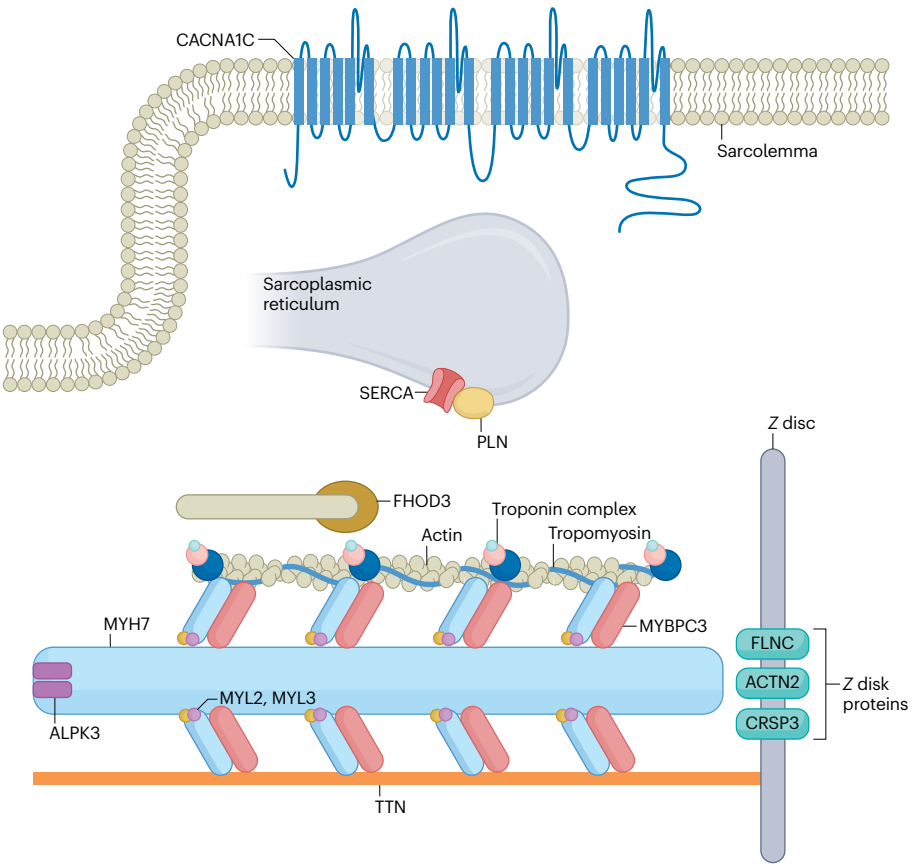

Fig. 3 | Genes involved in HCM pathophysiology. Genes that have been implicated in hypertrophic cardiomyopathy (HCM) pathophysiology encode proteins involved in cardiac muscle contraction. HCM-associated genes encoding proteins of the sarcoplasmic reticulum include *PLN* (phospholamban). Phospholamban regulates sarcoendoplasmic reticulum calcium ATPase (SERCA) activity. *CACNA1C* encodes a subunit of the voltage-gated calcium channel CaV1.2. Those genes encoding sarcomere proteins include *TTN*, *MYH7*, *MYBPC3*, *TPM1*, *MYL2* and *MYL3*, *ACTC1*, *TNNI3*, *TNNT2* and *TNNC1*. *ALPK3* encodes an essential cardiac pseudokinase that aids myosin-mediated force buffering and sarcomere proteostasis. *FHOD3* is a gene associated with HCM that encodes proteins involved in actin filament polymerization. Finally, *Z*-disk genes that have been linked to HCM include *FLNC*, *ACTN2* and *CRSP3*.

However, care must be taken when using *z*-scores to diagnose HCM, as there are inherent limitations, including the existence of many different published normative data, which can result in considerable variation in *z*-scores for the same patient, and a *z*-score >2 may not correlate with the accepted value of 15 mm as the diagnostic cut-off for adults[56]. Furthermore, no normative data are available for wall thickness other than for the basal interventricular septum or posterior wall, which may not necessarily represent the area of maximal wall thickness in an individual. There are no accepted diagnostic criteria for paediatric relatives of individuals with HCM, but the presence of an abnormal ECG or associated morphological abnormalities (such as mitral valve abnormalities and exaggerated systolic thickening) in a child relative with a maximal left ventricular wall thickness <2 *z*-scores should raise the suspicion of early phenotypic expression[4].

In addition to the diagnostic criteria for left ventricular hypertrophy, a phenotype-based scoring system has been proposed to predict a positive result in genetic testing for HCM. Key positive predictors include reverse curve morphology (a predominant mid-septal convexity towards the left ventricular cavity), early diagnosis (<45 years of age), a maximum left ventricular wall thickness of ≥20 mm, a family history of HCM and a family history of SCD. When all given predictors are present, the probability of positive genetic testing is approximately 80% (ref. 57).

Using CMR measurements and an artificial intelligence algorithm, demographic-adjusted thresholds for left ventricular hypertrophy have been proposed. These thresholds have been shown to reduce the number of HCM diagnoses in a population cohort with various comorbidities, while increasing the sensitivity in hypertrophy detection in a cohort of patients with HCM, particularly in women[58].

Diagnostic strategies

HCM may present with symptoms but is often diagnosed incidentally following an abnormal ECG detected during occupational or sports testing, or family screening after the discovery of an index case. A comprehensive diagnostic evaluation includes a detailed family history, electrocardiography, echocardiography, cardiac MRI and laboratory testing, including genetic analysis.

Electrocardiography in HCM. ECG changes, including deep Q waves and inverted T waves in the inferolateral leads, can precede the development of measurable hypertrophy. The majority of patients with HCM exhibit repolarization abnormalities, electrocardiographic signs of left ventricular hypertrophy, atrial enlargement and pseudo-necrosis Q waves[59]. Giant negative T waves in the precordial leads are characteristic of apical HCM[60]. Nevertheless, 5–10% of patients with HCM have a normal ECG, typically associated with milder phenotypes and more favourable outcomes[61]. Emerging deep learning algorithms for ECG interpretation show promise in enhancing screening and detection of HCM in large patient cohorts[62], as well as in reliably identifying patients with high-risk imaging features[63].

Several ECG features might suggest the presence of an HCM phenocopy[64]. For example, a short PR interval with right bundle

branch block can be found in Fabry disease, whereas in cases showing a Wolff–Parkinson–White preexcitation pattern, severe left ventricular hypertrophy and early atrioventricular block, PRKAG2 syndrome or Danon disease should be suspected. Finally, in elderly patients, the presence of low ECG voltages that are discordant with left ventricular hypertrophy, along with atrial fibrillation and atrioventricular block, can be suggestive of cardiac amyloidosis.

Multimodality imaging for HCM diagnosis. Multimodality imaging is instrumental in both the diagnosis and management of HCM (Table 2). Several imaging phenotypes have been described based on the various septal morphologies of HCM, with septal classifications including reverse curve (in 30–40% of cases), sigmoidal (40–50%) apical (10%) and neutral (10%) contour[65]. Among the various techniques, echocardiography remains the first-line imaging modality during initial evaluation and can be performed at rest or during the Valsalva manoeuver in the sitting and semi-supine positions and then on standing if no gradient is provoked, to detect LVOTO[4]. Postprandial exercise can also provoke higher LVOTO and is particularly useful in patients who report more severe symptoms after meals[66]. Exercise echocardiography is used to elicit an LVOT gradient in symptomatic patients without notable obstruction at rest or after other manoeuvers[4] and represents the most physiological way to elicit the LVOT gradient. In genetically positive but asymptomatic family members, echocardiography screening should

Table 2 | Multimodality imaging in HCM

Feature	Imaging techniques	Observations
Left ventricular wall thickness	Echocardiography Cardiac MRI	Precise values for left ventricular wall thickness are used in the HCM definition as well as the ESC SCD risk estimation calculator Distribution of hypertrophied segments defines HCM type and aids in planning septal reduction techniques Extreme concentric hypertrophy (wall thickness greater than 30–35 mm) can be suggestive of Danon disease or Pompe disease
Left ventricular myocardium tissue characterization	Cardiac MRI	Native T1 mapping can characterize the myocardium: high T1 can be the result of high ECV due to diffuse fibrosis or amyloid deposition; low T1 values can appear very early in Fabry cardiomyopathy T2 mapping can identify oedema as a sign of active injury or inflammation, which can correlate with low grade troponin release and worse prognosis[158] LGE presence, localization and extent are described and can aid arrhythmic risk stratification[159] LGE distribution in sarcomeric HCM usually follows the hypertrophied segments. Concentric diffuse subendocardial LGE is suggestive of cardiac amyloidosis. Inferolateral basal LGE distribution can be seen more often in Fabry disease than other HCM phenocopies
Right ventricular wall thickness	Echocardiography Cardiac MRI	Right ventricular hypertrophy is often substantial in cardiac amyloidosis and Fabry disease
Mitral valve and apparatus	Echocardiography Cardiac MRI	Mitral valve elongation (mainly the anterior leaflet) and systolic anterior motion contribute towards LVOTO. Dyskinesia of the aorto-mitral apparatus, including SAM of the elongated AMVL, can occur in very early disease stages[35] Anterior displacement of the papillary muscles as well as other possible anomalies of the mitral apparatus can be seen[160]
LVOTO	Echocardiography	Evaluated at rest or during provocative manoeuvers (such as Valsalva, standing, exercise or administration of sublingual nitrates); the value of LVOT gradient is a determinant of symptoms and is used as a component of the SCD risk calculator A maximum provoked peak LVOTO of ≥50 mmHg in symptomatic patients represents an indication for LVOTO reduction therapies
LVEF	Echocardiography Cardiac MRI	Usually, LVEF in HCM is normal or supra-normal (>65%) However, during the progression towards a heart failure phenotype (or 'burnout phase') LVEF can progressively decrease Left ventricular systolic dysfunction can occur in mitochondrial cardiomyopathy
Left ventricular longitudinal strain	Echocardiography	Longitudinal myocardial velocities and strain are usually abnormal especially at the level of the hypertrophied segments, with early changes during hypertrophy development An apical sparing pattern of GLS is suggestive of cardiac amyloidosis
Left ventricular diastolic function	Echocardiography	Diastolic dysfunction can be of grade I, II or III (ref. 161) Some patients with non-obstructive HCM develop a restrictive physiology phenotype or triphasic pattern with severe biatrial enlargement and heart failure with preserved ejection fraction
Left atrium	Echocardiography Cardiac MRI	Left atrium anteroposterior diameter is a marker of risk for both atrial and ventricular arrhythmias, being a part of the ESC SCD risk estimation calculator
Interatrial septum	Echocardiography Cardiac MRI	Hypertrophy of the interatrial septum and atrial walls is usually seen in cardiac amyloidosis
Pericardial fluid	Echocardiography Cardiac MRI	Pericardial effusion associated with left ventricular hypertrophy often appears in cardiac amyloidosis

AMVL, anterior mitral valve leaflet; ECV, extracellular volume; ESC, European Society of Cardiology; GLS, global longitudinal strain, HCM, hypertrophic cardiomyopathy; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; LVOTO, left ventricular outflow tract obstruction; SAM, systolic anterior motion; SCD, sudden cardiac death.

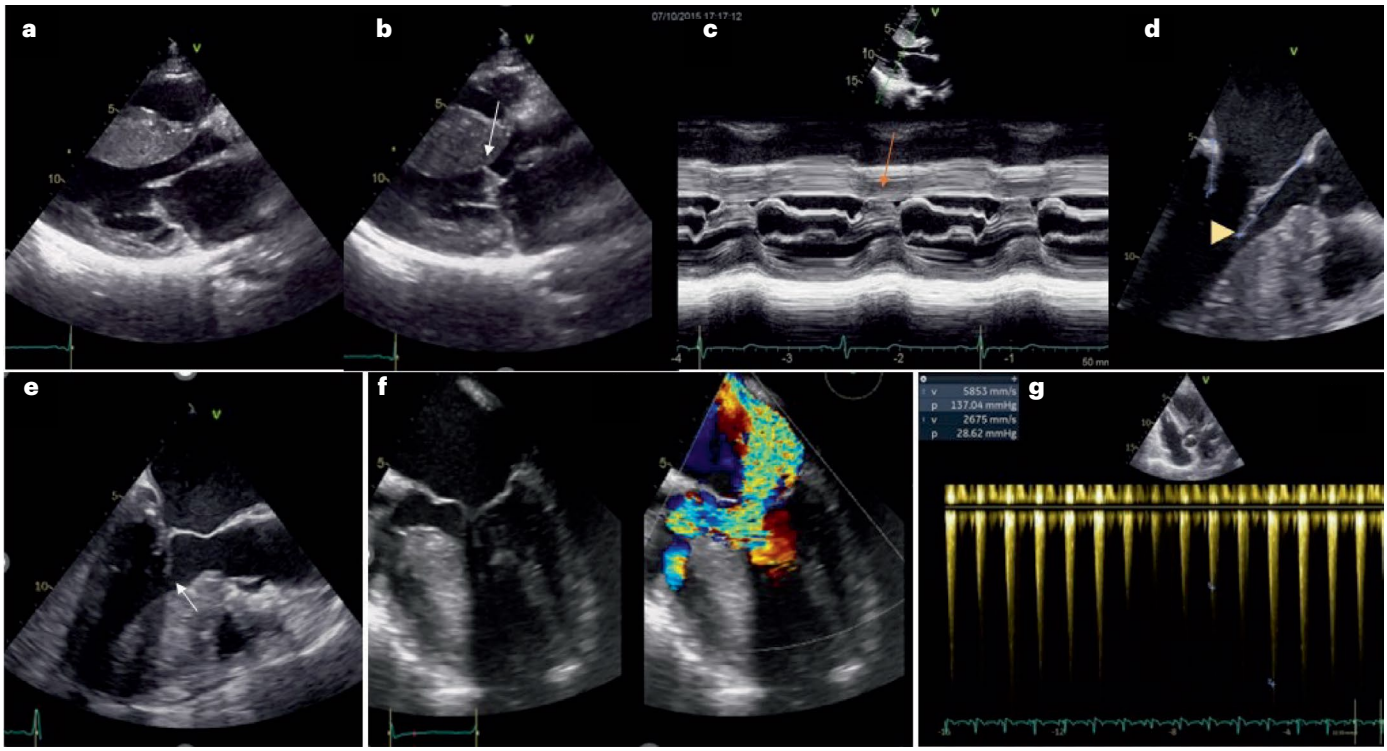

Fig. 4 | Echocardiographic features of a 32-year-old patient with obstructive hypertrophic cardiomyopathy. a, A parasternal long axis view of the heart showing asymmetric hypertrophy with an interventricular septum of 21 mm and posterior wall of 13 mm. **b**, Systolic frame from parasternal long axis view illustrating systolic anterior motion of the anterior mitral leaflet with septal contact (white arrow) leading to left ventricular outflow tract obstruction. **c**, M-mode from parasternal long axis view illustrating the contact interval between the anterior mitral leaflet and the interventricular septum (orange arrow). **d**,**e**, Mid-oesophageal view at 120° allows diastolic measurement of mitral leaflet lengths (21 mm for posterior leaflet, 34 mm for anterior leaflet) and illustrates the systolic anterior motion of the anterior mitral leaflet (yellow arrowhead and white arrow show the contact point of the mitral valve with the septum); panel **d** in diastole, panel **e** in systole. **f**, Mid-oesophageal view at 0° with simultaneous colour Doppler showing severe eccentric mitral regurgitation and systolic turbulence in the left ventricular outflow tract. **g**, A Doppler continuous wave aligned in the left ventricular outflow tract reveals a gradient at rest of 27 mmHg, increasing to 138 mmHg at Valsalva manoeuver.

be conducted regularly, beginning in childhood and continuing annually until age 18–21 years. Screening can be extended to every 5 years in adulthood[67].

Transoesophageal echocardiography should be considered in selected patients with LVOTO when the mechanism of obstruction is unclear or when a detailed assessment of the mitral valve is needed before septal reduction procedures — particularly if mitral regurgitation due to intrinsic valve abnormalities is suspected[4] (Fig. 4). Echocardiography also has an important role during septal reduction therapies. In alcohol septal ablation (ASA), for example, contrast echocardiography is used to identify the distribution of the target septal branches and their anatomical relation to the obstruction site.

CMR imaging is recommended for the assessment of myocardial structure and function, as well as for myocardial tissue characterization. It serves as a valuable tool for both diagnosis and risk stratification[4] (Table 2). CMR can help to identify HCM phenocopies such as Fabry disease or cardiac amyloidosis and can detect the presence of myocardial fibrosis and oedema (Fig. 5). Moreover, CMR may be considered in asymptomatic family members who test positive for HCM-associated genetic variants, enabling the detection of early disease features before echocardiography[4].

Genetic testing in HCM

Genetic testing involves not only variants in genes that encode components of the sarcomere but also genes associated with HCM phenocopies[39,68] (Table 3), such as *PRKAG2* (glycogen storage disease), *LAMP2* (Danon disease), *GLA* (Fabry disease) and *TTR* (variant transthyretin cardiac amyloidosis). Prompt identification of these aetiologies is important, as targeted therapies for several of these conditions are available[39,69].

Genetic testing is recommended in both the European and US guidelines for HCM[69,70]. The identification of pathogenic or likely pathogenic variants provides diagnostic clarity in the proband and the option of cascade genetic testing in family members. By contrast, the detection of a likely benign or benign variant does not warrant further genetic investigation, and clinical surveillance — typically involving an ECG and echocardiogram — is sufficient.

The presence of a VUS is not clinically actionable but could be investigated further in clinical or research settings to clarify variant pathogenicity. Regular re-evaluation is necessary, as a VUS may be reclassified over time. Genetic evaluation of patients with HCM and their families should be performed in specialized, multidisciplinary HCM centres, where counselling and clinical guidance can be

provided[70]. Genetic testing in children that are relatives of a proband is recommended after the age of 10–12 years, although earlier testing may be considered if there is a family history of early disease onset.

Differential diagnosis

Hypertensive heart disease can mimic HCM[71] but typically presents with only moderate left ventricular hypertrophy (less than 15 mm) that is usually concentric or mildly asymmetric (with a septal:posterior wall thickness of <1:3), differing from the more asymmetric forms found in HCM[72]. Of note, left ventricular thickness that is >15 mm has been reported in patients with chronic kidney disease or in healthy African American individuals. In athletes, HCM is suggested by a left ventricular wall thickness of >16 mm, especially with asymmetric, segmental hypertrophy, reduced left ventricular cavity size, left ventricular systolic dysfunction (including subclinical with decreased global longitudinal strain), diastolic dysfunction, left atrial enlargement, cryptae and/or mitral valve anomalies with systolic anterior motion and left ventricular obstruction[73]. Patients with moderate-to-severe valvular or sub/supravalvular aortic stenosis can also develop left ventricular hypertrophy over time. However, when the extent of hypertrophy is disproportionate to aortic stenosis severity, the possibility of concomitant aortic stenosis and HCM should be considered. In addition, transthyretin cardiac amyloidosis can occur in 10% of patients with aortic stenosis[74,75] and should be considered in the differential diagnosis.

Age at diagnosis is an important factor in the differential diagnosis of HCM. Early HCM onset, particularly in children that are <10 years of age, should raise suspicion for phenocopies, such as RASopathies, metabolic disorders and mitochondrial diseases. By contrast, the presence of red flags in later life, such as carpal tunnel syndrome or renal disease, suggests amyloidosis or Fabry disease[76]. The combination of multimodality imaging and genetic testing is a highly effective approach in distinguishing these differential diagnoses and establishing an accurate diagnosis.

Paediatric HCM

As in adults, most cases of childhood-onset HCM, including those presenting in preadolescence, are caused by pathogenic variants in genes

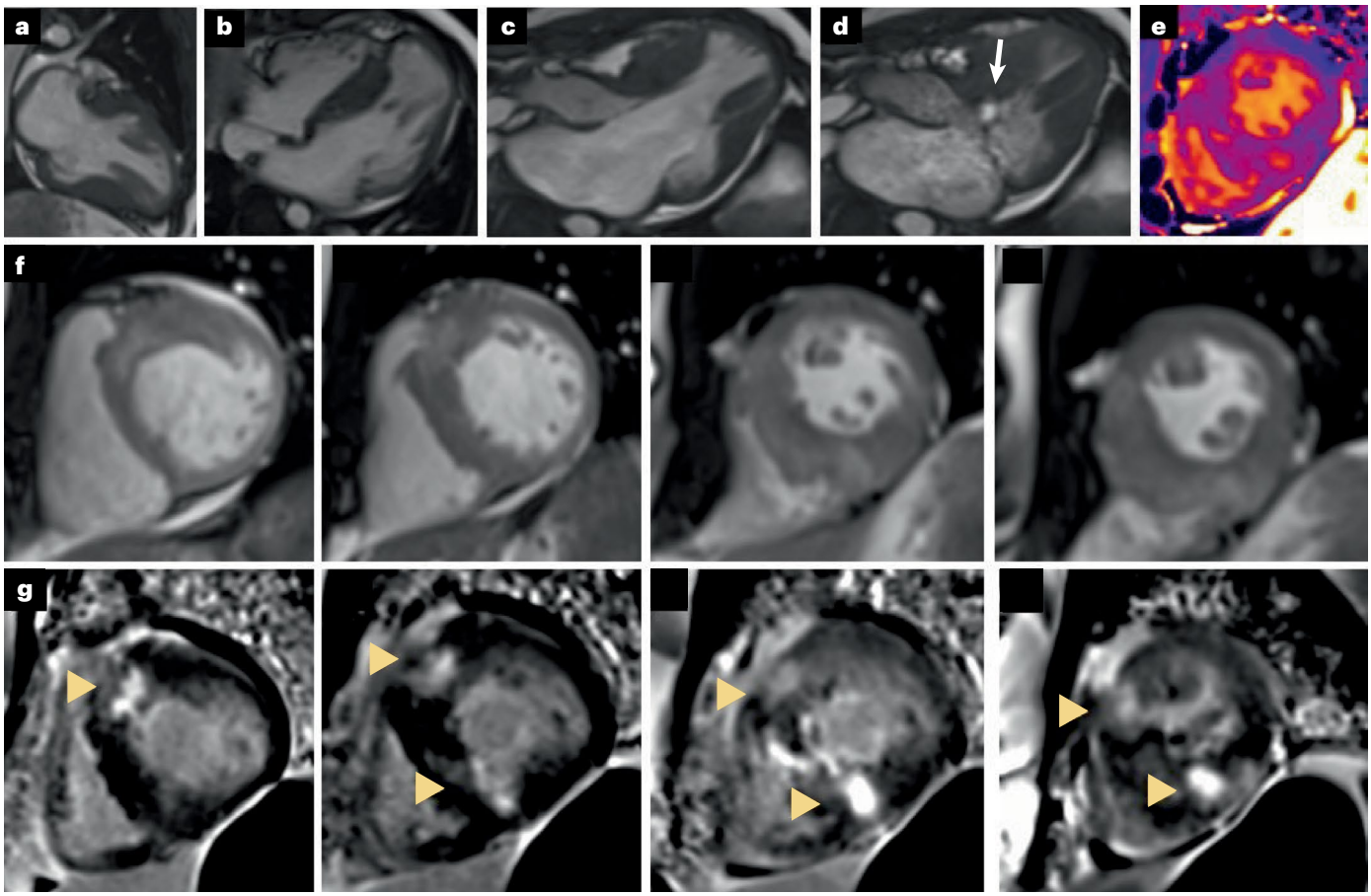

Fig. 5 | Contrast-enhanced cardiac MRI in a 26-year-old carrier of a *MYBPC3* variant. a–**c**, Balanced steady-state free procession cine sequences diastolic frames from two-chamber (part **a**), four-chamber (part **b**) and three-chamber (part **c**) views, showing left ventricular asymmetric hypertrophy as well as papillary muscle apical insertion. **d**, The systolic frame from a three-chamber view showing systolic anterior motion of the mitral leaflet with septal contact and subsequent systolic flow acceleration in the left ventricle outflow tract (white arrow). **e**, Native T1 mapping in short axis view showing increased T1 values in the hypertrophied myocardium but normal T1 values in the thin walls. **f**, Balanced steady-state free procession sequences of diastolic frames in short axis views at several ventricular levels illustrating the spiral distribution of hypertrophy from base (hypertrophy of anterior and anteroseptal walls) to apex (hypertrophy of inferoseptal and inferior walls) – important for myectomy planning. **g**, Late gadolinium enhancement (LGE) imaging in short axis views showing patchy areas of hyperenhancement (arrowheads), representing extensive myocardial fibrosis of the hypertrophied left ventricular walls.

Table 3 | Common 'HCM phenocopy' disease genes

Gene symbol	Gene name	Inheritance pattern	Disease	Treatments
PRKAG2	Protein kinase AMP-activated non-catalytic subunit-γ 2	AD	WPW syndrome	Antiarrhythmic drugs, WPW ablation
LAMP2	Lysosomal-associated membrane protein 2	X-linked	Danon disease	ICD implantation, early assessment for heart transplantation
GLA	Galactosidase-α	X-linked	Fabry disease	Chaperone therapy, enzyme-replacement therapies, antiplatelet or anticoagulant therapies, analgesics for symptomatic neuropathy
GAA	α-Glucosidase	AR	Pompe disease	Enzyme-replacement therapies, non-invasive ventilation
TTR	Transthyretin	AD	Transthyretin amyloidosis	Transthyretin stabilizers, antisense oligonucleotides, small interfering RNA, gene therapy, antibodies[162], heart failure support therapy, heart transplant

AD, autosomal dominant; AR, autosomal recessive; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter–defibrillator; WPW, Wolff–Parkinson–White.

encoding components of the cardiac sarcomere. These variants are typically inherited in an autosomal dominant manner and account for 55–75% of childhood-onset HCM cases beyond infancy (<1 year of age)[77]. Even in infant-onset HCM, sarcomeric disease accounts for up to 40% of cases[77,78] (Supplementary Fig. 1). Although previous international recommendations suggested that clinical expression of sarcomeric disease was rare below the age of 10–12 years, studies over the past 10 years have challenged this paradigm, demonstrating that sarcomeric HCM can be identified in child relatives in at least 10% of families with a known proband, and that early diagnosis can lead to meaningful changes in clinical management[79]. As a result, updated North American and European guidelines recommend clinical and genetic screening of paediatric first-degree relatives at any age, rather than waiting until adolescence[4,70].

By contrast, the aetiology of infant-onset HCM is highly heterogeneous. Over 30% of cases are caused by malformation syndromes (such as Noonan syndrome and associated RASopathies), inborn errors of metabolism (such as Pompe disease) and mitochondrial cytopathies[78] (Fig. 6). Neuromuscular disorders, such as Friedreich ataxia, more commonly manifest in adolescence[78]. A systematic approach to diagnostic work-up is required to identify clinical cardiac and extracardiac red flags that may point towards specific aetiological diagnoses (Supplementary Table 1) and guide appropriate management[4]. It is important to exclude potentially reversible causes (such as maternal gestational diabetes, twin–twin transfusion syndrome and neonatal corticosteroid use), as well as early-onset sarcomeric disease (including double or compound variants), even without a family history of HCM, which can progress to end-stage heart failure with poor survival beyond the first year of life. Noonan syndrome or a related RASopathy should be considered in infants with HCM and the presence of biventricular outflow tract obstruction along with at least one red flag for a neurocardiofaciocutaneous syndrome (such as dysmorphism and cutaneous or skeletal anomalies). Biventricular hypertrophy with systolic dysfunction can be a manifestation of an inborn error of metabolism, particularly in the presence of additional extracardiac red flags, such as hypotonia, elevated creatine kinase levels or parental consanguinity[80] (Fig. 7).

Natural history of paediatric HCM. HCM in children often presents at two extremes of a broad disease epectrum: a severe, early-onset, rapidly progressive form with poor prognosis and a milder phenotypic representing early expression of adult cardiomyopathy phenotypes, typically identified through family screening[4]. The natural history of childhood-onset HCM is highly dependent on the age at presentation and underlying aetiology. Children with inborn errors of metabolism and malformation syndromes often present with symptoms of heart failure in the first few months of life and have a very high mortality rate in the first 2 years, primarily due to heart failure-related death. By contrast, SCD is the most common cause of death in older children and adolescents with HCM[15,16,78]. The 5-year survival rates for childhood-onset HCM vary according to underlying aetiological groups and age of diagnosis (Supplementary Table 2). Importantly, in non-syndromic HCM, children diagnosed in preadolescence (<12 years of age) have similar outcomes and mortality rates to older teenagers[81]. Early cohort studies including patients younger than 18 years, reported SCD rates of up to 10% per year[82,83], but more recent population-based studies suggest annual SCD rates of 1.2–1.5% (refs. 16,84). Although substantially lower than previously thought, this rate is still approximately 50% higher than in adult-onset HCM[85]. Importantly, although most cases of SCD occur in children with variants in sarcomere genes, metabolic and syndromic HCM can also be associated with SCD[84,86], highlighting the importance of systematic risk stratification in all children with HCM. There is substantial lifelong morbidity and mortality associated with childhood-onset HCM, with the natural history curves shifted to the left compared with adult-onset disease and, in many cases, a more rapid rate of disease progression[48,81]. Furthermore, although SCD is the most common cause of death in children and adolescents with HCM, longer-term morbidity and mortality is largely related to heart failure, atrial fibrillation and stroke[48].

SCD risk prediction and prevention

SCD is one of the most dreaded complications of HCM, typically resulting from ventricular fibrillation or sustained ventricular tachycardia but occasionally associated with high-degree atrioventricular block[87]. Young individuals are at higher risk than older individuals, although SCD can occur at any age[88,89]. Although HCM was initially considered a leading cause of SCD in young athletes[90], more recent reports suggest it is a possible – but not the most common – underlying cause of these tragic events[91–93]. Follow-up studies of adult patients with HCM report an annual cardiovascular death rate of 1–2%, with SCD, heart failure and thromboembolism being the main causes of death[94].

European and American guidelines both recommend an ICD following a major arrhythmic event, such as ventricular fibrillation-driven cardiac arrest or sustained ventricular tachycardia, but differ in their

recommendations for primary prevention[4,70]. The European guidelines rely on the validated HCM Risk-SCD tool, which incorporates variables such as age, maximal wall thickness, left atrial diameter, left ventricular outflow tract gradient, family history of SCD, non-sustained ventricular tachycardia and unexplained syncope, and provides a linear regression risk score to predict SCD event rates at 5 years of follow-up. The American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend an ICD for primary prevention in the presence of at least one major clinical marker, including apical aneurysms, extensive late gadolinium enhancement at cardiac MRI and LVEF ≤50%, which are given less weight in the European Society of Cardiology (ESC) guidelines. These differences have considerable repercussions on the ICD implantation rates, which are higher in the USA than in Europe[95]. One study suggested a lower rate of appropriate ICD therapy in US centres than in non-US sites, consistent with a lower-risk population, and no significant difference in the rate of SCD in US sites compared with non-US sites[95]. Furthermore, the ACC/AHA guidelines propose the use of the HCM Risk-SCD tool in support of a shared decision-making process for ICD implantation, whereas the same tool appears more centre-staged and is the first step for SCD prevention according to ESC guidelines[4,70].

The HCM Risk-SCD model has excellent specificity but low sensitivity, and its application across different ethnicities — particularly in the North American populations — may be suboptimal[96]. In a study evaluating the performance of the AHA/ACC and ESC HCM guidelines in a Japanese cohort, both performed well in stratifying patients with HCM, but the 2024 AHA/ACC guidelines performed better than the 2023 ESC guidelines in differentiating SCD risk between patients with class IIa and those with class IIb indications[97]. Further research is needed to identify the optimal strategy for SCD prevention. Importantly, strategies aimed at preventing SCD in HCM should consider competing risks, such as advanced age and comorbidities, which impact on the general life expectancy of the individual and therefore on the choice of whether to implant an ICD[98].

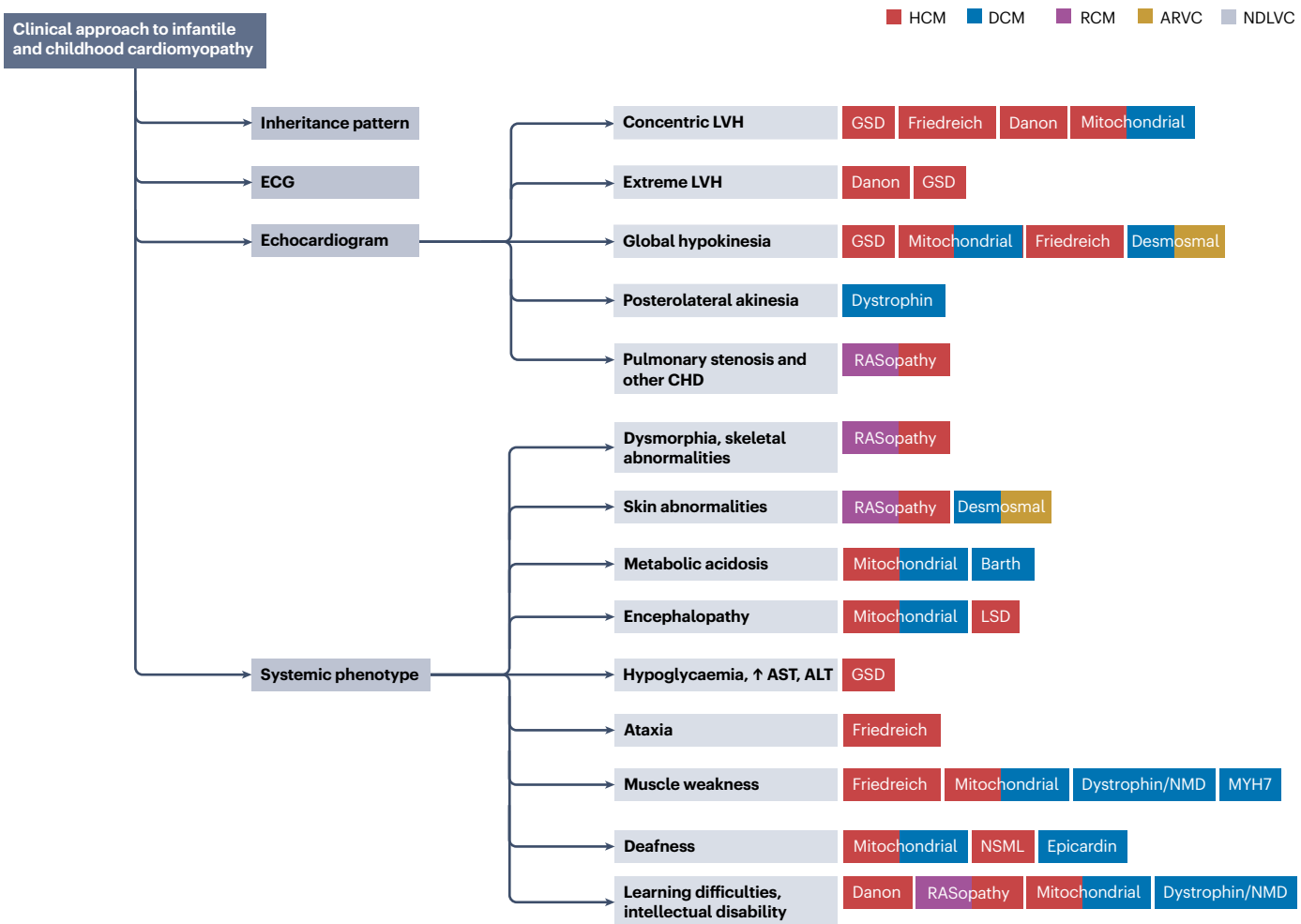

Fig. 6 | Diagnostic workflow for infant-onset HCM. In infant- and childhood-onset cardiomyopathy, echocardiography and systemic features can help determine the aetiology of hypertrophic cardiomyopathy (HCM). ARVC, arrhythmogenic right ventricular cardiomyopathy; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CHD, congenital heart disease; DCM, dilated cardiomyopathy; ECG, electrocardiogram; GSD, glycogen storage disorder; LSD, lysosomal storage disease; LVH, left ventricular hypertrophy; NDLVC, non-dilated left ventricular cardiomyopathy; NMD, neuromuscular disease; NSML, Noonan syndrome with multiple lentigines; RCM, restrictive cardiomyopathy. The figure was adapted with permission from ref. 4, Oxford University Press.

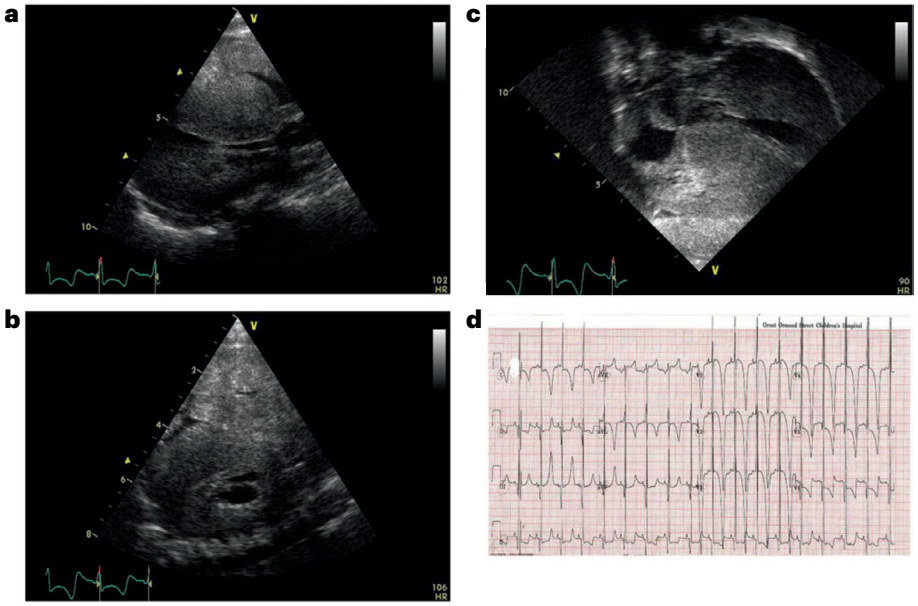

Fig. 7 | Electrocardiogram and echocardiography of a child with Pompe disease. Echocardiographic and electrocardiographic characteristics of a patient with Pompe disease. **a**, Parasternal long axis view showing severe ventricular hypertrophy. **b**,**c**, Parasternal short axis view (panel **b**) and subcostal view (panel **c**) showing severe biventricular hypertrophy. **d**, Electrocardiography trace showing short PR, signs of biventricular hypertrophy and marked repolarization abnormalities. The figure was reprinted with permission from ref. 80, BMJ.

Most patients with HCM who receive an ICD are exposed to long-term ICD-related issues, due to their typically long life expectancy and active lifestyles. A subcutaneous ICD offers the opportunity to avoid complications associated with the intracardiac leads of transvenous ICDs. Therefore, when the risk of bradyarrhythmias and/or T wave oversensing is deemed low, subcutaneous ICDs are a reliable option for safe and effective termination of potentially life-threatening ventricular tachyarrhythmias[99].

ICD implantation is recommended in European and North American guidelines for patients with HCM that have previously experienced malignant ventricular arrhythmia-related cardiac arrest[4,70], and over 60% of patients undergoing ICD implantation in secondary prevention received an appropriate ICD therapy within 5 years of follow-up[100]. The identification of individuals who could benefit from primary prevention ICD implantation is more challenging and a major aspect of the clinical management of childhood-onset HCM. The approach to risk stratification in paediatric HCM has changed substantially in the past decade, with the development of paediatric-specific risk prediction models. Previous European (and current American) guidelines recommended the use of individual risk factors, largely extrapolated from adult data, to identify children at high risk of SCD, by providing relative (rather than absolute) estimates of risk[4,70], but the accuracy of this approach is poor[101]. In 2019, the first paediatric-specific risk prediction model was developed, using clinical parameters (maximal left ventricular wall thickness *z*-score, left atrial diameter *z*-score, left ventricular outflow tract gradient, presence of non-sustained ventricular tachycardia and unexplained syncope) to provide a personalized estimate of SCD risk at 5 years follow-up[102]. This model (HCM Risk-Kids) has been externally validated[103] and incorporated into European guidelines as the recommended method to evaluate risk in children <16 years of age with HCM (class I, level of evidence B), as part of shared decision-making discussions with patients and families[4]. A second paediatric model (PRIMaCY)[104] offers similar discriminatory ability but has poorer calibration compared with HCM Risk-Kids, potentially leading to overestimation of risk in some patients[105]. The development of paediatric-specific risk prediction models is a major advance in childhood-onset HCM prognostic stratification. Future research will attempt to refine the performance of these models and provide real-world validation.

Sports participation

Sports participation was traditionally discouraged in patients with HCM, and competitive sports were categorically prohibited in all patients with HCM[106,107]. The recommendation to avoid sports participation found its roots in autopsy studies on young athletes who died suddenly, which reported a high prevalence of HCM at postmortem examination[90]. Later studies challenged this notion, emphasizing that SCD in athletes could be due to a plethora of cardiac conditions, of which HCM does not seem to be the most common[91–93,108,109]. Furthermore, current evidence shows that physical activity should be promoted in patients with HCM. No excess of SCD was seen in athletes with HCM who continued to exercise[110,111]. Notably, no difference emerged in appropriate ICD discharges between recreational activity and competitive sport, although appropriate and inappropriate shocks were more common during physical activity than at rest. However, these studies were underpowered to assess the true impact of vigorous exercise, and although sports that involve explosive sprints, such as basketball and soccer, were included, a low number of athletes participated in sports with high risk of collision, such as American football or ice hockey. The Lifestyle and Exercise in HCM (LIVE-HCM) prospective registry included a large cohort of exercising patients with HCM that presented no increased risk of SCD or life-threatening arrhythmias with vigorous or moderate exercise compared with those who were sedentary[112]. The RESET-HCM trial randomized 136 patients with HCM to 16 weeks of moderate-intensity exercise training or usual activity. Moderate exercise seemed to be safe in these patients, with a small increase in exercise capacity at 16 weeks (1.35 (95% confidence interval (CI) 0.50 to 2.21) ml/kg/min versus 0.08 (95% CI −0.62 to 0.79) ml/kg/min)[113].

The heterogeneous morphology and pathophysiology of HCM means that some individuals can safely participate in vigorous exercise,

including high-intensity competitive sports. Recent guidelines have embraced a more liberal stance, supporting a shared decision-making approach in the absence of clinical markers indicating elevated risk[114,115]. This shift is particularly important as the risk perception of patients can be influenced by many factors. Indeed, because the paternalistic approach has been replaced with a physician–patient relationship based on autonomy in which patients can decide on how much physical activity they undergo, subjectivity of risk becomes relevant[116].

Pregnancy

Pregnancy, contraception and the heritability of HCM are sensitive matters that require expert counselling and management in specialized centres. Most women with HCM tolerate pregnancy well, and data suggest that most pregnancies occur before HCM diagnosis[117,118]. The incidence of maternal death and neonatal death in HCM is as low as 0.2% for each end point, similar to patients without HCM[119]. However, patients with New York Heart Association (NYHA) functional class ≥II or signs of heart failure are at higher risk of adverse events during pregnancy, and the development of severe heart failure during pregnancy is associated with death or advanced heart failure over 20 years of follow-up[117,120], with no significant differences between women with obstructive and non-obstructive HCM[117]. Notably, pregnancy-related increase in plasma volume and left ventricular dimensions might reduce LVOTO and result in a favourable haemodynamic effect. Pregnant women with HCM should be monitored by a multidisciplinary team with expertise in high-risk pregnancies. Frequency of follow-up is determined by the risk according to the World Health Organization classification[121] and should include at least one echocardiographic assessment per trimester. Finally, caesarian section has historically been overutilized in women with HCM; current consensus recommends it should be confined to obstetric indications[70].

Management

Therapeutic approaches for LVOTO

For decades, nonspecific negative inotropes (drugs that decrease the force of cardiac contraction such as the sodium channel blocker disopyramide) and/or chronotropes (drugs that lower the heart rate, including non-vasodilating β-blockers, non-dihydropyridine calcium channel blockers (CCBs)) have been the mainstay of LVOTO treatment[122,123] (Table 4). Treatment with the β-blocker metoprolol is associated with a reduction in LVOT gradient and the degree of mitral regurgitation and with improvements in dyspnoea and angina but no change in maximum exercise capacity (peak VO_2)[124,125]. Non-dihydropyridine CCBs can be used when β-blockers are poorly tolerated or minimally effective[70]. Notably, in patients with very high resting LVOT gradient (for example >100 mmHg), CCBs should be avoided due to the possible vasodilator effect[115]. Disopyramide is a safe and effective class Ia antiarrhythmic drug, used as an add-on therapy to β-blockers or CCBs, and acts as a negative inotrope via inhibition of multiple ionic channels[126]. However, almost 40% of patients with obstructive HCM are still symptomatic on β-blockers or calcium channel blockers ± disopyramide[127] and may become candidates for septal myectomy (surgical reduction of the hypertrophied septum) or ASA. In young patients, including those with multiple abnormalities requiring surgical correction, myectomy represents the gold standard[4], with the potential to provide radical relief of obstruction and mitral regurgitation, as well as of symptoms. ASA is preferred in fragile patients with a high risk of surgery-related complications or when surgical expertise is not available. Relief of LVOT gradient is less radical and predictable compared with surgery, one-third of patients may need repeated procedures, and it is associated with increased long-term all-cause mortality compared with septal myectomy[4,128].

Septal myectomy leads to reverse myocardial remodelling with left ventricular mass reduction[129], with a 10-year survival similar to the general age-matched population, and in experienced centres, the operative mortality is as low as 0.4–0.8% (ref. 130). However, safety and efficacy vary dramatically depending on patient volume at each centre, with many centres performing suboptimally due to limited expertise[115]. Notably, septal reduction therapies — myectomy and ASA — do not impact the subsequent progression of the cardiomyopathic process, and in a subset of patients, severe left ventricular dysfunction can develop 10–20 years after even optimal procedural results[131].

Myosin inhibitors

Allosteric cardiac myosin inhibitors, such as mavacamten and aficamten, are a novel class of drugs specifically developed to counteract excessive sarcomere activation and normalize contractility in HCM. Phase II and III clinical trials have shown consistent efficacy in terms of functional capacity, symptoms and LVOTO in adult patients with HCM (Fig. 8 and Supplementary Tables 3–5); studies on non-obstructive HCM and paediatric patients are underway[132,133].

Mavacamten proved safe and effective in patients with obstructive HCM classified as NYHA class II–IV (refs. 132,134). Treatment was associated with an improvement in functional capacity, symptom burden and a sustained reduction in LVOT gradient and cardiac biomarkers. A small decrease in LVEF was observed, and 6% of patients experienced a transient LVEF reduction to below 50% (refs. 132,134). Mavacamten is approved by both the FDA and EMA for patients with obstructive HCM and NYHA class II/III. The EMA requires genotyping for *CYP2C19* — which encodes an enzyme important for drug metabolism — as poor metabolizers may have up to threefold greater mavacamten exposure. Special warnings for mavacamten have been reported by the FDA and EMA (Supplementary Box 1).

Following the 2023 ESC guidelines, mavacamten administration should be considered in addition to β-blockers or CCBs or as monotherapy when other therapeutic options are unable to improve symptoms in patients with obstructive HCM. By contrast, septal reduction therapy is reserved for patients who do not respond to pharmaceutical therapies[4]. For patients with persistent symptoms despite β-blocker or CCB treatment, an update to the AHA guidelines recommends adding a myosin inhibitor, disopyramide or septal reduction therapy performed at experienced centres[115].

Aficamten is a next-in-class myosin inhibitor with some potential advantages over mavacamten, including a shorter half-life, faster titration schedule, a shallow dose–response curve and less propensity for drug–drug interaction[135] (Supplementary Table 6). In the SEQUOIA-HCM trial, aficamten resulted in a greater improvement in peak VO_2 compared with placebo, with consistent results across prespecified subgroups, including those on β-blocker. All secondary endpoints were met, with a reduction in LVOT gradients evident after 2 weeks, which was associated with a decrease in cardiac biomarkers. A transient reduction to below 50% in LVEF occurred in five patients receiving aficamten and in one patient in the placebo group; however, none required interruption of treatment due to heart failure[133] (Supplementary Table 7).

Despite understandable enthusiasm, several important questions remain regarding the use of myosin inhibitors in clinical practice. Specifically, approximately 30% of patients in clinical trials continued to exhibit LVOT gradients[136], and predictors of therapeutic response are

Table 4 | Commonly used drugs for treating HCM

Drug	Indication	Mechanism of action	Adverse effects	Notes
Nadolol	Symptomatic treatment of LVOTO Rate control in AF VT	Non-selective block of β1 and β2 adrenergic receptors Negative chronotropic, inotropic and dromotropic effects Blocks peak sodium current, reducing the risk for delayed afterdepolarizations	Chronotropic incompetence, AV conduction prolongation, asthma	Hydrophilic, long acting (24 h half-life) non-selective β-blocker β-Blocker of choice in LQTS and CPVT
Metoprolol	Symptomatic treatment of LVOTO Rate control in AF VT	Selective block of β1 adrenergic receptors Negative chronotropic, inotropic, and dromotropic effects	Chronotropic incompetence, AV conduction slowing, asthma	Reduces LVOT obstruction at rest and during exercise Provides symptom relief, and improves quality of life in patients with obstructive HCM Half-life: 3–7 h
Bisoprolol	Heart failure with reduced ejection fraction	Selective block of β1 adrenergic receptors Negative chronotropic, inotropic and dromotropic effects	Chronotropic incompetence, AV conduction slowing, asthma	Generally well tolerated
Verapamil	Symptomatic treatment of LVOTO Rate control in AF	Non-dihydropyridine calcium channel blocker Negative inotropic, chronotropic and dromotropic effects	AV conduction slowing	Potentially harmful due to vasodilating effect in severe LVOTO (>100 mmHg) and congestive heart failure
Diltiazem	Symptomatic treatment of LVOTO Rate control in AF	Non-dihydropyridine calcium channel blocker Inhibits the entry of calcium ions into slow L-type calcium channels Negative inotropic, chronotropic and dromotropic effects	AV conduction slowing	Less prominent vasodilator and myocardial depressant compared with verapamil
Disopyramide	Symptomatic treatment of LVOTO in association with β-blockers or CCBs AF rhythm control Control of SVT, NSVT or ventricular ectopic beats	Class I antiarrhythmic Multichannel inhibition Negative inotropic effect, action potential shortening and reduction of early and afterdepolarizations	QT interval prolongation, dry mouth (xerostomy), accommodative disturbances (inability of the eyes to focus clearly on nearby objects), lower urinary tract symptoms and prostatism	Safe and well tolerated
Amiodarone	AF rhythm control, control of SVT, NSVT, or ventricular ectopic beats	Class III antiarrhythmic Multichannel inhibition	QTc prolongation, photosensitivity, thyroid dysfunction, pulmonary interstitial disease	Incomplete efficacy for SCD prevention despite reduction of NSVT
Sotalol	Prevent recurrence of sustained VT or ventricular fibrillation Rhythm control in AF	Non-selective β-blocker and class III antiarrhythmic Multichannel inhibition	QTc prolongation, fatigue, bradycardia proarrhythmia (APD prolongation and delayed afterdepolarization induction), asthma	Modest success on cardioversion of AF[163]
Flecainide	Rhythm control in AF Prevention of ventricular arrhythmias, ventricular ectopic beats	Class Ic antiarrhythmic Frequency-dependent blockade of Na^+ channels	Prolonged QT, AV conduction slowing, organization of atrial fibrillation into atrial flutter and facilitation of 1:1 conduction (cotreatment with β-blocker recommended)	Contraindicated in heart failure and ischaemic heart disease Not generally recommended in the absence of an ICD
Mavacamten (negative inotrope)	LVOTO	Myosin inhibitor	Pharmacodynamic interactions, contraindicated in pregnancy	Long half-life (6–9 days)

AF, atrial fibrillation; APD, action potential duration; AV, atrioventricular; CCB, calcium channel blocker; CPVT, catecholaminergic polymorphic ventricular tachycardia; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter–defibrillator; LVOTO, left ventricular outflow tract obstruction; LQTS, long QT syndrome; NSVT, non-sustained ventricular tachycardia; QTc, corrected QT interval; SCD, sudden cardiac death; SVT, sustained ventricular tachycardia; VT, ventricular tachycardia. The data are from ref. 164.

yet to be defined. Furthermore, long-term efficacy and safety, effects on children and across ethnicities, as well as the disease-modifying potential and effect on long-term outcomes remain undefined. Ultimately, myosin inhibitors require continuous administration, and its high cost may limit accessibility.

When discussing treatments with patients who have symptomatic obstructive HCM, a detailed explanation of both septal reduction therapies and pharmaceutical options is important. This includes highlighting the choice between a one-time invasive intervention and a continuous treatment that requires constant monitoring but could

potentially modify the natural history of the disease. For women of childbearing age, treatment with myosin inhibitors should be combined with effective contraceptive measures due to its teratogenic risk. In addition, we emphasize that interrupting treatment could exacerbate symptoms and trigger heart failure.

New approaches for non-obstructive HCM

In non-obstructive HCM, hypercontractility, small left ventricular cavity and diastolic dysfunction can lead to elevated intraventricular pressures and reduced stroke volume. Several therapeutic approaches have been tested and are under investigation (Supplementary Table 8).

The phase II MAVERICK-HCM trial showed a reduction in circulating NTproBNP and troponin I (markers of heart failure and myocardial damage) in patients with non-obstructive HCM treated with mavacamten[137]. However, the subsequent phase III trial (ODYSSEY-HCM) did not meet the composite primary end point – a change from baseline to week 48 in the Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-23 CSS) and peak oxygen consumption – compared with the placebo (NCT05582395). In cohort 4 of the REDWOOD HCM trial, patients with non-obstructive HCM treated with aficamten had improved symptoms, quality of life and cardiac biomarkers. Three patients (8%) had LVEF <50% without signs of heart failure, and no patient discontinued the treatment due to severe adverse events[138]. The phase 3 trial ACACIA-HCM will evaluate the efficacy and safety of Aficamten compared with the placebo in adults with symptomatic non-obstructive HCM (NCT06081894), including patients with mid-ventricular obstruction.

In the phase II IMPROVE-HCM trial (NCT04826185), 67 patients with non-obstructive HCM were randomized to ninerafaxstat, a novel cardiac mitotrope (a drug that improves cardiac function by altering mitochondrial activity) or placebo. Ninerafaxstat was reported to be safe and well tolerated, with treatment associated with better ventilatory efficiency (VE/VCO2 slope) compared with the placebo[139].

SGLT2 inhibitors are safe and effective in reducing the risk of heart failure progression and cardiovascular death across the entire spectrum of heart failure phenotypes. However, patients with HCM have been excluded from RCTs[140]. The mechanism underlying the cardiac benefit of SGLT2 is still unknown; however, an improvement in cardiomyocyte metabolic homoeostasis, as well as antinflammatory and nephroprotective effects, have been hypothesized[141]. Preliminary data showed a potential benefit of SGLT2 inhibitors in patients with HCM. In an open label clinical trial of patients with diabetes and non-obstructive HCM, 6 months treatment with SGLT2 inhibitors was associated with improvements in diastolic function and 6 min walking distance[142]. In addition, a propensity score matching analysis revealed that patients with HCM treated with SGLT2 inhibitors compared with a control population of patients with HCM not receiving SGLT2 inhibitors had a lower risk of all-cause mortality[143].

Sotagliflozin is an SGLT2 inhibitor that also provides some gastrointestinal SGLT1 inhibition. Its efficacy in improving quality of life will be evaluated in a phase III study involving patients with both obstructive and non-obstructive HCM (NCT06481891).

Quality of life

HCM is often associated with a substantial symptom burden that can markedly impair quality of life. In a recent Dutch study, quality of life (measured by the KCCQ, EQ-D5-DL and EQ-VAS questionnaires) was lower in patients with HCM compared with both genotype positive-phenotype negative patients and the general population[144]. Notably, patients with

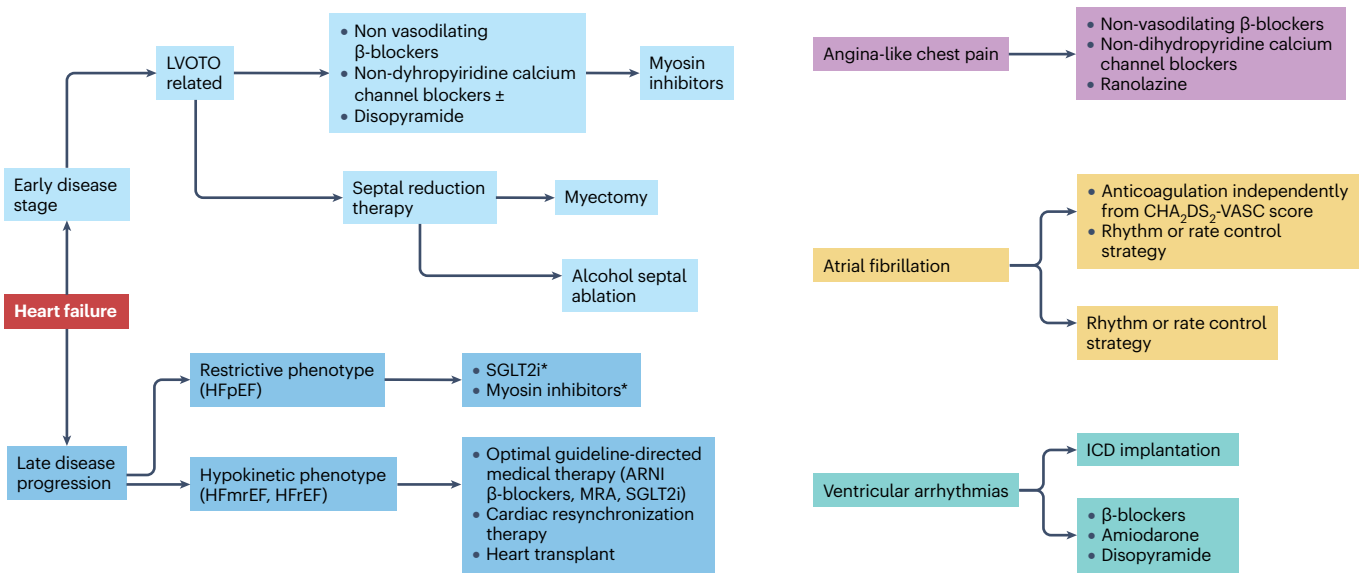

Fig. 8 | Summary of hypertrophic cardiomyopathy therapeutic options. Heart failure due to left ventricular outflow tract obstruction (LVOTO) may be treated with pharmacological therapies or septal reduction therapies (light blue boxes). In the case of heart failure with preserved ejection fraction (HFpEF), SGLT2 inhibitors (SGLT2i) and myosin inhibitors are currently under study in ongoing clinical trials (denoted by an asterisk). Heart failure with reduced or mildly reduced ejection fraction (HFrEF or HFmrEF) should be treated with guideline-directed medical therapy (dark blue boxes). Antianginal therapy can be used in case of chest pain (purple boxes). Patients with atrial fibrillation should receive anticoagulation, and a rhythm control or rate control strategy can be used based on the clinical characteristics of the patient (yellow boxes). In the case of ventricular arrhythmias, the options include antiarrhythmic drugs and implantable cardioverter–defibrillator (ICD) implantation (green boxes). ARNI, angiotensin receptor-neprilysin inhibitor; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74 and Sc (sex category, female); MRA, mineralocorticoid receptor antagonist.

obstructive HCM reported lower quality of life scores compared with patients with non-obstructive HCM, women reported lower scores compared with men and the lowest quality of life was evident in younger HCM patients[144]. A HCM diagnosis was also associated with high societal costs, driven predominantly by healthcare costs and productivity losses[144].

The KCCQ has been validated in patients with obstructive HCM[145] and used in the EXPLORER-HCM and SEQUOIA-HCM studies — two phase three trials that evaluated the effectiveness of cardiac myosin inhibitors in HCM. In the EXPLORER-HCM trial, after 30 weeks of treatment, the change in KCCQ overall summary score was greater with mavacamten than placebo (difference + 9.1, 95% CI 5.5 to 12.8), indicating a larger improvement in quality of life, with similar benefits across all KCCQ subscales[146]. Notably, around 30% of patients on the myosin inhibitor felt no differently or worse compared with baseline. In the SEQUOIA-HCM trial, treatment with the myosin inhibitor aficamten improved both the mean KCCQ overall summary score (difference 7.9, 95% CI 4.8 to 11.0) and Seattle Angina Questionnaire (SAQ7-SS, difference: 7.8; 95% CI 4.7 to 11.0) at 24 weeks, compared with placebo. A total of 37% of patients on aficamten showed no difference or worsening of their quality of life status. Recognizing the importance of patient-reported outcomes as endpoints in clinical trials, KCCQ has been chosen as primary end point in ODYSSEY-HCM, ACACIA-HCM and SONATA-HCM.

Symptoms are one of the main determinants of quality of life. To capture the spectrum of symptoms that are typical of HCM, such as shortness of breath, tiredness and fatigue, palpitation, chest pain, dizziness and syncope, the HCM Symptom Questionnaire has been developed[147]. The HCM Symptom Questionnaire is sensitive to changes in symptoms[147], and in the EXPLORER-HCM trial, patients on mavacamten compared with placebo showed an improvement in the shortness of breath domain (change from baseline −1.8, 95% CI −2.4 to −1.2, clinically meaningful score reduction >2.5)[132].

Outlook

Gene therapy

Gene therapy, defined as the use of genetic material as a therapeutic tool, represents a new frontier of targeted therapies for HCM[148]. Gene therapy techniques include gene replacement (delivery of a functional copy of a defective gene) or gene editing (direct modification of a targeted native DNA sequence). For gene therapy to be effective, the genetic material needs to be delivered into the target cells using an appropriate vector. Currently, due to their cardiotropism and low immunogenicity, adeno-associated viruses (AAV) are the most commonly used vectors in cardiology. Gene editing tools include CRISPR–Cas9 technology and can introduce double-stranded or single-stranded breaks at specific DNA sites, enabling the conversion, deletion or insertion of DNA nucleobases[148].

Gene replacement. Gene replacement techniques are being investigated for the treatment of Danon Disease and MYBPC3-related HCM. Danon disease is caused by loss of function variants in the X chromosome gene *LAMP2* that lead to LAMP2B deficiency, macroautophagy impairment and the development of severe, paediatric-onset HCM in male patients[149]. RP-A501 (an AAV9-delivering *LAMP2B* transgene) safety and toxicity have been evaluated in a phase I trial in male patients with Danon disease. The results of this trial reveal that *LAMP2B* expression is associated with improved cardiac histology, improvement or stabilization of clinical status and reduction of left ventricular hypertrophy and cardiac biomarkers of heart failure and myocardial damage. Adverse events included thrombotic microangiopathy and hepatotoxicity[150–152].

Preliminary data from *Mybpc3*$^{-/-}$ mice show that TN-201 (an AAV9-delivering *MYBPC3* transgene) restored wild-type levels of cardiac MYBPC3 protein, which was correctly incorporated in the sarcomere, prolonging the lifespan of treated mice[153]. Since October 2023, three patients participating in the MyPeak-1 phase Ib clinical trial evaluating the safety and tolerability of a one-time intravenous infusion of TN-201 have been dosed and the trial is ongoing[154].

Gene editing. In humanized mouse models of HCM, intrathoracic injection of a dual AAV9 delivery system — containing an adenine base editing system, a Cas9 nickase and guide RNA targeting the *MYH7* pathogenic missense variant p.Arg403Gln — successfully corrected the allele and reversed or prevented the pathological phenotype[155,156]. In humans, great steps forward have been made in the field of gene therapy with exciting preliminary data, although gene therapy infusion is not risk free. The gene therapy product can trigger the immune system, potentially causing liver toxicity, myocarditis and thrombotic microangiopathy, necessitating a potent immunosuppressive regimen. Furthermore, the duration of the therapeutic effect and long-term consequences are still unknown. HCM can remain clinically stable for years, presenting two major challenges for clinical trial design: selecting an effective end point that captures treatment-associated effects within a time frame compatible with a clinical trial and identifying candidates at risk of adverse outcomes, that are not too advanced in their disease stage. Further natural history studies are needed to develop precise disease trajectory models that could guide future clinical trials[157].

Several questions remain unanswered in HCM. From a diagnostic standpoint, sex-specific, race-specific and age-specific diagnostic criteria are still lacking, making diagnosis particularly challenging in women, minority ethnic groups and children. The reasons behind variable penetrance and incomplete expressivity in HCM also remain unclear. Genome-wide association studies and an improved understanding of the role of environmental factors could be key to elucidating these phenomena. Genotype-specific and phenotype-specific natural history studies could help clarify disease progression and identify potential predictors of adverse outcomes. The diagnostic and prognostic role of cardiac biomarkers is yet to be fully defined; therefore, their routine collection in clinical practice and registry data should be encouraged. SCD is rare in HCM, although it can occur in patients without established risk factors. A deep phenotyping of these cases could help identify risk markers and improve risk stratification.

HCM is a highly heterogeneous disease in terms of aetiology, clinical presentation, natural history and outcomes. Understanding this complexity is key for accurate risk stratification and effective clinical management. Although a truly individualized molecular approach is still evolving, personalized care — including symptom control, family screening, lifestyle counselling, pregnancy and family planning, as well as prevention of disease-related complications — is increasingly achievable. The advent of cardiac myosin inhibitors, by targeting the core pathophysiological abnormality of HCM, is the first truly innovative step towards precision medicine for patients with HCM. Although many open questions remain, mysosin inhibitors are rapidly establishing themselves as a new treatment standard, not as an alternative but rather as a complement to therapies developed over the last five decades. Establishing dedicated centres of excellence, where traditional and new therapeutic options are available, represents the best support for patients with HCM and their families.

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References

1. Semsarian, C., Ingles, J., Maron, M. S. & Maron, B. J. New perspectives on the prevalence of hypertrophic cardiomyopathy. *J. Am. Coll. Cardiol.* **65**, 1249–1254 (2015).
2. Hespe, S. et al. Genes associated with hypertrophic cardiomyopathy: a reappraisal by the ClinGen Hereditary Cardiovascular Disease Gene Curation Expert Panel. *J. Am. Coll. Cardiol.* **85**, 727–740 (2025).
3. Ho, C. Y. et al. Genotype and lifetime burden of disease in hypertrophic cardiomyopathy: insights from the sarcomeric human cardiomyopathy registry (SHaRe). *Circulation* **138**, 1387–1398 (2018).
   Seminal work from the SHaRe registry in which the clinical characteristics and prognosis of genotype positive and genotype negative patients are described.
4. Arbelo, E. et al. 2023 ESC guidelines for the management of cardiomyopathies. *Eur. Heart J.* **44**, 3503–3626 (2023).
   The ESC guidelines that include the experts' recommendation for diagnosis and treatment of hypertrophic cardiomyopathy.
5. Massera, D., Sherrid, M. V., Maron, M. S., Rowin, E. J. & Maron, B. J. How common is hypertrophic cardiomyopathy… really?: disease prevalence revisited 27 years after CARDIA. *Int. J. Cardiol.* **382**, 64–67 (2023).
6. Massera, D. et al. Prevalence of unexplained left ventricular hypertrophy by cardiac magnetic resonance imaging in MESA. *JAHA* **8**, e012250 (2019).
7. Butzner, M. et al. Clinical diagnosis of hypertrophic cardiomyopathy over time in the United States (a population-based claims analysis). *Am. J. Cardiol.* **159**, 107–112 (2021).
8. De Marvao, A. et al. Phenotypic expression and outcomes in individuals with rare genetic variants of hypertrophic cardiomyopathy. *J. Am. Coll. Cardiol.* **78**, 1097–1110 (2021).
9. Butters, A., Lakdawala, N. K. & Ingles, J. Sex differences in hypertrophic cardiomyopathy: interaction with genetics and environment. *Curr. Heart Fail. Rep.* **18**, 264–273 (2021).
10. van Driel, B., Nijenkamp, L., Huurman, R., Michels, M. & van der Velden, J. Sex differences in hypertrophic cardiomyopathy: new insights. *Curr. Opin. Cardiol.* **34**, 254–259 (2019).
11. Wells, S., Rowin, E. J., Bhatt, V., Maron, M. S. & Maron, B. J. Association between race and clinical profile of patients referred for hypertrophic cardiomyopathy. *Circulation* **137**, 1973–1975 (2018).
12. Eberly, L. A. et al. Association of race with disease expression and clinical outcomes among patients with hypertrophic cardiomyopathy. *JAMA Cardiol.* **5**, 83–91 (2020).
13. Tjahjadi, C. et al. Differences in characteristics and outcomes between patients with hypertrophic cardiomyopathy from Asian and European centers. *JAHA* **11**, e023313 (2022).
14. Arola, A. et al. Epidemiology of idiopathic cardiomyopathies in children and adolescents. A nationwide study in Finland. *Am. J. Epidemiol.* **146**, 385–393 (1997).
15. Nugent, A. W. et al. The epidemiology of childhood cardiomyopathy in Australia. *N. Engl. J. Med.* **348**, 1639–1646 (2003).
16. Lipshultz, S. E. et al. The incidence of pediatric cardiomyopathy in two regions of the United States. *N. Engl. J. Med.* **348**, 1647–1655 (2003).
17. Braunwald, E. Hypertrophic cardiomyopathy: the early years. *J. Cardiovasc. Trans. Res.* **2**, 341–348 (2009).
18. Braunwald, E. Hypertrophic cardiomyopathy: the first century 1869–1969. *Glob. Cardiol. Sci. Pract.* **2012**, 5 (2012).
19. Morita, H. et al. Shared genetic causes of cardiac hypertrophy in children and adults. *N. Engl. J. Med.* **358**, 1899–1908 (2008).
20. Watkins, H. et al. Characteristics and prognostic implications of myosin missense mutations in familial hypertrophic cardiomyopathy. *N. Engl. J. Med.* **326**, 1108–1114 (1992).
21. Lehman, S. J., Crocini, C. & Leinwand, L. A. Targeting the sarcomere in inherited cardiomyopathies. *Nat. Rev. Cardiol.* **19**, 353–363 (2022).
22. Kawana, M., Sarkar, S. S., Sutton, S., Ruppel, K. M. & Spudich, J. A. Biophysical properties of human β-cardiac myosin with converter mutations that cause hypertrophic cardiomyopathy. *Sci. Adv.* **3**, e1601959 (2017).
23. Helms, A. S. et al. Effects of MYBPC3 loss-of-function mutations preceding hypertrophic cardiomyopathy. *JCI Insight* **5**, e133782 (2020).
24. Helms, A. S. et al. Spatial and functional distribution of *MYBPC3* pathogenic variants and clinical outcomes in patients with hypertrophic cardiomyopathy. *Circ: Genom. Precis. Med.* **13**, 396–405 (2020).
   Study evaluating the distribution of *MYBPC3* variants and clinical outcomes of patients with these variants.
25. Pettinato, A. M. et al. Development of a cardiac sarcomere functional genomics platform to enable scalable interrogation of human *TNNT2* variants. *Circulation* **142**, 2262–2275 (2020).
26. Madan, A. et al. *TNNT2* mutations in the tropomyosin binding region of TNT1 disrupt its role in contractile inhibition and stimulate cardiac dysfunction. *Proc. Natl Acad. Sci. USA* **117**, 18822–18831 (2020).
27. Teekakirikul, P. et al. Cardiac fibrosis in mice with hypertrophic cardiomyopathy is mediated by non-myocyte proliferation and requires Tgf-β. *J. Clin. Invest.* **120**, 3520–3529 (2010).
28. Coleman, J. A., Ashkir, Z., Raman, B. & Bueno-Orovio, A. Mechanisms and prognostic impact of myocardial ischaemia in hypertrophic cardiomyopathy. *Int. J. Cardiovasc. Imaging* **39**, 1979–1996 (2023).
29. Aguiar Rosa, S., Rocha Lopes, L., Fiarresga, A., Ferreira, R. C. & Mota Carmo, M. Coronary microvascular dysfunction in hypertrophic cardiomyopathy: pathophysiology, assessment, and clinical impact. *Microcirculation* **28**, e12656 (2021).
30. Ranjbarvaziri, S. et al. Altered cardiac energetics and mitochondrial dysfunction in hypertrophic cardiomyopathy. *Circulation* **144**, 1714–1731 (2021).
31. Nollet, E. E. et al. Mitochondrial dysfunction in human hypertrophic cardiomyopathy is linked to cardiomyocyte architecture disruption and corrected by improving NADH-driven mitochondrial respiration. *Eur. Heart J.* **44**, 1170–1185 (2023).
32. Santini, L., Coppini, R. & Cerbai, E. Ion channel impairment and myofilament Ca^{2+} sensitization: two parallel mechanisms underlying arrhythmogenesis in hypertrophic cardiomyopathy. *Cells* **10**, 2789 (2021).
33. Coppini, R. et al. Electrophysiological and contractile effects of disopyramide in patients with obstructive hypertrophic cardiomyopathy. *JACC Basic. Transl. Sci.* **4**, 795–813 (2019).
34. Ayoub, C. et al. Comparison of valsalva maneuver, amyl nitrite, and exercise echocardiography to demonstrate latent left ventricular outflow obstruction in hypertrophic cardiomyopathy. *Am. J. Cardiol.* **120**, 2265–2271 (2017).
35. Sherrid, M. V., Gunsburg, D. Z., Moldenhauer, S. & Pearle, G. Systolic anterior motion begins at low left ventricular outflow tract velocity in obstructive hypertrophic cardiomyopathy. *J. Am. Coll. Cardiol.* **36**, 1344–1354 (2000).
36. Ergi, D. G. et al. Changes in left ventricular-aortic angulation are associated with the development of obstruction in hypertrophic cardiomyopathy. *J. Thorac. Cardiovasc. Surg.* **170**, 190–199 (2025).
37. Sawma, T. et al. Outcomes of septal myectomy in patients with obstructive hypertrophic cardiomyopathy and minimal septal hypertrophy. *J. Thor. Cardiovasc. Surg.* https://doi.org/10.1016/j.jtcvs.2025.02.024 (2025).
38. on behalf of the ACMG Laboratory Quality Assurance Committee. et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American college of medical genetics and genomics and the Association for molecular pathology. *Genet. Med.* **17**, 405–423 (2015).
39. Marian, A. J. & Braunwald, E. Hypertrophic cardiomyopathy: genetics, pathogenesis, clinical manifestations, diagnosis, and therapy. *Circ. Res.* **121**, 749–770 (2017).
40. Meisner, J. K. et al. Low penetrance sarcomere variants contribute to additive risk in hypertrophic cardiomyopathy. *Circulation* https://doi.org/10.1161/CIRCULATIONAHA.124.069398 (2024).
   A study that explains how low penetrance sarcomere variants influence HCM expression.
41. Harper, A. R. et al. Common genetic variants and modifiable risk factors underpin hypertrophic cardiomyopathy susceptibility and expressivity. *Nat. Genet.* **53**, 135–142 (2021).
42. Joy, G. et al. Microstructural and microvascular phenotype of sarcomere mutation carriers and overt hypertrophic cardiomyopathy. *Circulation* **148**, 808–818 (2023).
43. Hughes, R. K. et al. Myocardial perfusion defects in hypertrophic cardiomyopathy mutation carriers. *JAHA* **10**, e020227 (2021).
44. Captur, G. et al. The embryological basis of subclinical hypertrophic cardiomyopathy. *Sci. Rep.* **6**, 27714 (2016).
45. Joy, G., Moon, J. C. & Lopes, L. R. Detection of subclinical hypertrophic cardiomyopathy. *Nat. Rev. Cardiol.* **20**, 369–370 (2023).
46. Joy, G. et al. Electrophysiological characterization of subclinical and overt hypertrophic cardiomyopathy by magnetic resonance imaging-guided electrocardiography. *J. Am. Coll. Cardiol.* **83**, 1042–1055 (2024).
47. Fourey, D. et al. Prevalence and clinical implication of double mutations in hypertrophic cardiomyopathy: revisiting the gene-dose effect. *Circ. Cardiovasc. Genet.* **10**, e001685 (2017).
48. Marston, N. A. et al. Clinical characteristics and outcomes in childhood-onset hypertrophic cardiomyopathy. *Eur. Heart J.* **42**, 1988–1996 (2021).
49. Olivotto, I., Cecchi, F., Poggesi, C. & Yacoub, M. H. Patterns of disease progression in hypertrophic cardiomyopathy: an individualized approach to clinical staging. *Circ: Heart Fail.* **5**, 535–546 (2012).
50. Topriceanu, C.-C., Pereira, A. C., Moon, J. C., Captur, G. & Ho, C. Y. Meta-analysis of penetrance and systematic review on transition to disease in genetic hypertrophic cardiomyopathy. *Circulation* https://doi.org/10.1161/CIRCULATIONAHA.123.065987 (2023).
51. Lorenzini, M. et al. Penetrance of hypertrophic cardiomyopathy in sarcomere protein mutation carriers. *J. Am. Coll. Cardiol.* **76**, 550–559 (2020).
52. Pelliccia, F. et al. Long-term outcome of nonobstructive versus obstructive hypertrophic cardiomyopathy: a systematic review and meta-analysis. *Int. J. Cardiol.* **243**, 379–384 (2017).
53. Marstrand, P. et al. Hypertrophic cardiomyopathy with left ventricular systolic dysfunction: insights from the SHaRe registry. *Circulation* **141**, 1371–1383 (2020).
   Study showing clinical characteristics and outcomes of patients with left ventricular systolic dysfunction.
54. Fumagalli, C. et al. Incidence of stroke in patients with hypertrophic cardiomyopathy in stable sinus rhythm during long-term monitoring. *Int. J. Cardiol.* **381**, 70–75 (2023).
55. Coppini, R. et al. Clinical phenotype and outcome of hypertrophic cardiomyopathy associated with thin-filament gene mutations. *J. Am. Coll. Cardiol.* **64**, 2589–2600 (2014).
56. Kaski, J. P. et al. Indications and management of implantable cardioverter-defibrillator therapy in childhood hypertrophic cardiomyopathy. *Cardiol. Young-.* **33**, 681–698 (2023).
57. Bos, J. M. et al. Characterization of a phenotype-based genetic test prediction score for unrelated patients with hypertrophic cardiomyopathy. *Mayo Clin. Proc.* **89**, 727–737 (2014).
58. Shiwani, H. et al. Demographic-based personalized left ventricular hypertrophy thresholds for hypertrophic cardiomyopathy diagnosis. *J. Am. Coll. Cardiol.* **85**, 685–695 (2025).

59. Biagini, E. et al. Usefulness of electrocardiographic patterns at presentation to predict long-term risk of cardiac death in patients with hypertrophic cardiomyopathy. *Am. J. Cardiol.* **118**, 432–439 (2016).
60. Hughes, R. K. et al. Apical hypertrophic cardiomyopathy: the variant less known. *JAHA* **9**, e015294 (2020).
61. Delcrè, S. D. L. et al. Relationship of ECG findings to phenotypic expression in patients with hypertrophic cardiomyopathy: a cardiac magnetic resonance study. *Int. J. Cardiol.* **167**, 1038–1045 (2013).
62. Sangha, V. et al. Identification of hypertrophic cardiomyopathy on electrocardiographic images with deep learning. Preprint at *medrXiv* https://doi.org/10.1101/2023.12.23.23300490 (2023).
63. Carrick, R. T. et al. Identification of high-risk imaging features in hypertrophic cardiomyopathy using electrocardiography: a deep-learning approach. *Heart Rhythm* https://doi.org/10.1016/j.hrthm.2024.01.031 (2024).
64. Rapezzi, C. et al. Diagnostic work-up in cardiomyopathies: bridging the gap between clinical phenotypes and final diagnosis. A position statement from the ESC working group on myocardial and pericardial diseases. *Eur. Heart J.* **34**, 1448–1458 (2013).
65. Bos, J. M., Towbin, J. A. & Ackerman, M. J. Diagnostic, prognostic, and therapeutic implications of genetic testing for hypertrophic cardiomyopathy. *J. Am. Coll. Cardiol.* **54**, 201–211 (2009).
66. La Canna, G. et al. Phenotyping left ventricular obstruction with postprandial re-test echocardiography in hypertrophic cardiomyopathy. *Am. J. Cardiol.* **125**, 1688–1693 (2020).
67. Maron, B. J. et al. Diagnosis and evaluation of hypertrophic cardiomyopathy. *J. Am. Coll. Cardiol.* **79**, 372–389 (2022).
68. Pieroni, M. et al. Beyond sarcomeric hypertrophic cardiomyopathy: how to diagnose and manage phenocopies. *Curr. Cardiol. Rep.* https://doi.org/10.1007/s11886-022-01778-2 (2022).
69. Wilde, A. A. M. et al. European heart rhythm association (EHRA)/Heart rhythm society (HRS)/Asia pacific heart rhythm society (APHRS)/Latin American heart rhythm society (LAHRS) expert consensus statement on the state of genetic testing for cardiac diseases. *J. Arrhythmia* **38**, 491–553 (2022).
70. Writing Committee Members. 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* **142**, e533–e557 (2020).
71. Perrone-Filardi, P. et al. Non-invasive cardiovascular imaging for evaluating subclinical target organ damage in hypertensive patients. *Eur. Heart J. Cardiovasc. Imaging* **18**, 945–960 (2017).
72. Cardim, N. et al. Role of multimodality cardiac imaging in the management of patients with hypertrophic cardiomyopathy: an expert consensus of the European association of cardiovascular imaging endorsed by the Saudi heart association. *Eur. Heart J. Cardiovasc. Imaging* **16**, 280–280 (2015).
73. D'Andrea, A. et al. The role of multimodality imaging in athlete's heart diagnosis: current status and future directions. *JCM* **10**, 5126 (2021).
74. Nitsche, C. et al. Prevalence and outcomes of concomitant aortic stenosis and cardiac amyloidosis. *J. Am. Coll. Cardiol.* **77**, 128–139 (2021).
75. Scully, P. R. et al. Prevalence and outcome of dual aortic stenosis and cardiac amyloid pathology in patients referred for transcatheter aortic valve implantation. *Eur. Heart J.* **41**, 2759–2767 (2020).
76. Kaski, J. P. et al. Cardiomyopathies in children and adolescents: aetiology, management, and outcomes in the European society of cardiology EURObservational research programme cardiomyopathy and myocarditis registry. *Eur. Heart J.* https://doi.org/10.1093/eurheartj/ehae109 (2024).
A study evaluating clinical charateristics and outcomes of children and adolescents with cardiomyopathies.
77. Kaski, J. P. et al. Prevalence of sarcomere protein gene mutations in preadolescent children with hypertrophic cardiomyopathy. *Circ. Cardiovasc. Genet.* **2**, 436–441 (2009).
78. Norrish, G. et al. Clinical presentation and long-term outcomes of infantile hypertrophic cardiomyopathy: a European multicentre study. *Esc. Heart Fail.* **8**, 5057–5067 (2021).
79. Norrish, G. et al. Yield of clinical screening for hypertrophic cardiomyopathy in child first-degree relatives. *Circulation* **140**, 184–192 (2019).
80. Moak, J. P. & Kaski, J. P. Hypertrophic cardiomyopathy in children. *Heart* **98**, 1044–1054 (2012).
81. Norrish, G. et al. Clinical features and natural history of preadolescent nonsyndromic hypertrophic cardiomyopathy. *J. Am. Coll. Cardiol.* **79**, 1986–1997 (2022).
82. McKenna, W. J. & Deanfield, J. E. Hypertrophic cardiomyopathy: an important cause of sudden death. *Arch. Dis. Child.* **59**, 971–975 (1984).
83. Yetman, A. T., Hamilton, R. M., Benson, L. N. & McCrindle, B. W. Long-term outcome and prognostic determinants in children with hypertrophic cardiomyopathy. *J. Am. Coll. Cardiol.* **32**, 1943–1950 (1998).
84. Norrish, G. et al. Clinical presentation and survival of childhood hypertrophic cardiomyopathy: a retrospective study in United Kingdom. *Eur. Heart J.* **40**, 986–993 (2019).
85. O'Mahony, C. et al. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM Risk-SCD). *Eur. Heart J.* **35**, 2010–2020 (2014).
86. Lynch, A. et al. Risk of sudden death in patients with RASopathy hypertrophic cardiomyopathy. *J. Am. Coll. Cardiol.* **81**, 1035–1045 (2023).
87. Maron, B. J. et al. Management of hypertrophic cardiomyopathy: JACC state-of-the-art review. *J. Am. Coll. Cardiol.* **79**, 390–414 (2022).
88. Maron, B. J. et al. Hypertrophic cardiomyopathy in children, adolescents, and young adults associated with low cardiovascular mortality with contemporary management strategies. *Circulation* **133**, 62–73 (2016).
89. Finocchiaro, G. et al. Sudden cardiac death during exercise in young individuals with hypertrophic cardiomyopathy. *JACC Clin. Electrophysiol.* **9**, 865–867 (2023).
90. Maron, B. J., Doerer, J. J., Haas, T. S., Tierney, D. M. & Mueller, F. O. Sudden deaths in young competitive athletes: analysis of 1866 deaths in the United States, 1980–2006. *Circulation* **119**, 1085–1092 (2009).
91. Finocchiaro, G. et al. Etiology of sudden death in sports: insights from a United Kingdom regional registry. *J. Am. Coll. Cardiol.* **67**, 2108–2115 (2016).
92. Finocchiaro, G. et al. Sudden cardiac death among adolescents in the United Kingdom. *J. Am. Coll. Cardiol.* **81**, 1007–1017 (2023).
93. Petek, B. J. et al. Sudden cardiac death in National collegiate athletic association athletes: a 20-year study. *Circulation* **149**, 80–90 (2024).
94. Elliott, P. M. Historical trends in reported survival rates in patients with hypertrophic cardiomyopathy. *Heart* **92**, 785–791 (2005).
95. Nauffal, V. et al. Worldwide differences in primary prevention implantable cardioverter defibrillator utilization and outcomes in hypertrophic cardiomyopathy. *Eur. Heart J.* **42**, 3932–3944 (2021).
96. Wang, J. et al. Variable and limited predictive value of the European society of cardiology hypertrophic cardiomyopathy sudden-death risk model: a meta-analysis. *Can. J. Cardiol.* **35**, 1791–1799 (2019).
97. Amano, M. et al. Validation of guideline recommendation on sudden cardiac death prevention in hypertrophic cardiomyopathy. *JACC: Heart Fail.* **13**, 1014–1026 (2025).
98. Finocchiaro, G. et al. Sudden cardiac death in cardiomyopathies: acting upon 'acceptable' risk in the personalized medicine era. *Heart Fail. Rev.* **27**, 1749–1759 (2022).
99. Maron, M. S. et al. Evidence that subcutaneous implantable cardioverter-defibrillators are effective and reliable in hypertrophic cardiomyopathy. *JACC Clin. Electrophysiol.* **6**, 1019–1021 (2020).
100. Norrish, G. et al. Clinical outcomes and programming strategies of implantable cardioverter-defibrillator devices in paediatric hypertrophic cardiomyopathy: a UK national cohort study. *EP Europace* **23**, 400–408 (2021).
101. Norrish, G. et al. A validation study of the European society of cardiology guidelines for risk stratification of sudden cardiac death in childhood hypertrophic cardiomyopathy. *EP Europace* **21**, 1559–1565 (2019).
102. Norrish, G. et al. Development of a novel risk prediction model for sudden cardiac death in childhood hypertrophic cardiomyopathy (HCM Risk-Kids). *JAMA Cardiol.* **4**, 918–927 (2019).
103. Norrish, G. et al. External validation of the HCM Risk-Kids model for predicting sudden cardiac death in childhood hypertrophic cardiomyopathy. *Eur. J. Prev. Cardiol.* **29**, 678–686 (2022).
104. Miron, A. et al. A validated model for sudden cardiac death risk prediction in pediatric hypertrophic cardiomyopathy. *Circulation* **142**, 217–229 (2020).
105. Norrish, G. et al. Performance of the PRIMaCY sudden death risk prediction model for childhood hypertrophic cardiomyopathy: implications for implantable cardioverter-defibrillator decision-making. *Europace* **25**, euad330 (2023).
106. Pelliccia, A. et al. Recommendations for participation in competitive sport and leisure-time physical activity in individuals with cardiomyopathies, myocarditis and pericarditis. *Eur. J. Cardiovasc. Prev. Rehabil.* **13**, 876–885 (2006).
107. Maron, B. J. et al. Recommendations for physical activity and recreational sports participation for young patients with genetic cardiovascular diseases. *Circulation* **109**, 2807–2816 (2004).
108. Finocchiaro, G., Papadakis, M., Sharma, S. & Sheppard, M. Sudden cardiac death. *Eur. Heart J.* **38**, 1280–1282 (2017).
109. Corrado, D., Basso, C., Rizzoli, G., Schiavon, M. & Thiene, G. Does sports activity enhance the risk of sudden death in adolescents and young adults? *J. Am. Coll. Cardiol.* **42**, 1959–1963 (2003).
110. Pelliccia, A. et al. Clinical outcomes in adult athletes with hypertrophic cardiomyopathy: a 7-year follow-up study. *Br. J. Sports Med.* **54**, 1008–1012 (2020).
111. Lampert, R. et al. Safety of sports for athletes with implantable cardioverter-defibrillators: results of a prospective, multinational registry. *Circulation* **127**, 2021–2030 (2013).
112. Lampert, R. et al. Vigorous exercise in patients with hypertrophic cardiomyopathy. *JAMA Cardiol.* https://doi.org/10.1001/jamacardio.2023.1042 (2023).
A study showing that vigorous exercise in patients with HCM was not associated with an increased risk of adverse outcomes.
113. Saberi, S. et al. Effect of moderate-intensity exercise training on peak oxygen consumption in patients with hypertrophic cardiomyopathy: a randomized clinical trial. *JAMA* **317**, 1349–1357 (2017).
114. Pelliccia, A. et al. 2020 ESC guidelines on sports cardiology and exercise in patients with cardiovascular disease. *Eur. Heart J.* **42**, 17–96 (2021).
115. Ommen, S. R. et al. 2024 AHA/ACC/AMSSM/HRS/PACES/SCMR guideline for the management of hypertrophic cardiomyopathy. *J. Am. Coll. Cardiol.*https://doi.org/10.1016/j.jacc.2024.02.014 (2024).
AHA/ACC guidelines for the diagnosis and management of HCM.
116. Magavern, E. F., Finocchiaro, G., Sharma, S., Papadakis, M. & Borry, P. Time out: ethical reflections on medical disqualification of athletes in the context of mandated pre-participation cardiac screening. *Br. J. Sports Med.* **52**, 1207–1210 (2018).
117. Goland, S. et al. Pregnancy in women with hypertrophic cardiomyopathy: data from the European society of cardiology initiated registry of pregnancy and cardiac disease (ROPAC). *Eur. Heart J.* **38**, 2683–2690 (2017).

118. Fumagalli, C. et al. Impact of pregnancy on the natural history of women with hypertrophic cardiomyopathy. *Eur. J. Prev. Cardiol.* **31**, 3–10 (2024).
119. Moolla, M. et al. Outcomes of pregnancy in women with hypertrophic cardiomyopathy: a systematic review. *Int. J. Cardiol.* **359**, 54–60 (2022).
120. Musumeci, M. B. et al. Clinical course of pregnancy and long-term follow-up after delivery in hypertrophic cardiomyopathy. *J. Am. Coll. Cardiol.* **77**, 1262–1264 (2021).
121. Regitz-Zagrosek, V. et al. 2018 ESC guidelines for the management of cardiovascular diseases during pregnancy. *Eur. Heart J.* **39**, 3165–3241 (2018).
122. Ammirati, E. et al. Pharmacological treatment of hypertrophic cardiomyopathy: current practice and novel perspectives: pharmacological treatment of HCM. *Eur. J. Heart Fail.* **18**, 1106–1118 (2016).
123. Argirò, A. et al. Stage-specific therapy for hypertrophic cardiomyopathy. *Eur. Heart J. Suppl.* **25**, C155–C161 (2023).
124. Dybro, A. M. et al. Randomized trial of metoprolol in patients with obstructive hypertrophic cardiomyopathy. *J. Am. Coll. Cardiol.* **78**, 2505–2517 (2021).
125. Dybro, A. M. et al. Effects of metoprolol on exercise hemodynamics in patients with obstructive hypertrophic cardiomyopathy. *J. Am. Coll. Cardiol.* **79**, 1565–1575 (2022).
126. Adler, A. et al. Safety of outpatient initiation of disopyramide for obstructive hypertrophic cardiomyopathy patients. *JAHA* **6**, e005152 (2017).
127. Bertero, E. et al. Real-world candidacy to mavacamten in a contemporary hypertrophic obstructive cardiomyopathy population. *Eur. J. Heart Fail.* **26**, 59–64 (2024).
128. Cui, H. et al. Survival following alcohol septal ablation or septal myectomy for patients with obstructive hypertrophic cardiomyopathy. *J. Am. Coll. Cardiol.* **79**, 1647–1655 (2022).
129. Lu, G. et al. Left ventricle myocardial remodeling following septal myectomy in patients with hypertrophic obstructive cardiomyopathy. *J. Cardiovasc. Magn. Reson.* **27**, 101864 (2025).
130. Maron, M. S. et al. Outcomes over follow-up ≥10 years after surgical myectomy for symptomatic obstructive hypertrophic cardiomyopathy. *Am. J. Cardiol.* **163**, 91–97 (2022).
131. Maurizi, N. et al. Long-term outcomes after septal reduction therapies in obstructive hypertrophic cardiomyopathy: insights from the SHARE registry. *Circulation* https://doi.org/10.1161/CIRCULATIONAHA.124.069378 (2024).
132. Olivotto, I. et al. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* **396**, 759–769 (2020).
Randomized clinical trial that showed that the myosin inhibitor mavacamten was safe and effective in the treatment of obstructive HCM.
133. Maron, M. S. et al. Aficamten for symptomatic obstructive hypertrophic cardiomyopathy. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa2401424 (2024).
Randomized clinical trial that showed that the myosin inhibitor aficamten was safe and effective in the treatment of obstructive HCM.
134. Desai, M. Y. et al. Mavacamten in patients with hypertrophic cardiomyopathy referred for septal reduction: week 56 results from the VALOR-HCM randomized clinical trial. *JAMA Cardiol.* **8**, 968 (2023).
135. Chuang, C. et al. Discovery of aficamten (CK-274), a next-generation cardiac myosin inhibitor for the treatment of hypertrophic cardiomyopathy. *J. Med. Chem.* **64**, 14142–14152 (2021).
136. Desai, M. Y. et al. Real-world experience with mavacamten in obstructive hypertrophic cardiomyopathy: observations from a tertiary care center. *Prog. Cardiovasc. Dis.* https://doi.org/10.1016/j.pcad.2024.02.001 (2024).
137. Ho, C. Y. et al. Evaluation of mavacamten in symptomatic patients with nonobstructive hypertrophic cardiomyopathy. *J. Am. Coll. Cardiol.* **75**, 2649–2660 (2020).
138. Masri, A. et al. Efficacy and safety of aficamten in symptomatic non-obstructive hypertrophic cardiomyopathy: results from the REDWOOD-HCM trial, cohort 4. *J. Card. Fail.* https://doi.org/10.1016/j.cardfail.2024.02.020 (2024).
139. Maron, M. S. et al. Safety and efficacy of metabolic modulation with ninerafaxstat in patients with nonobstructive hypertrophic cardiomyopathy. *J. Am. Coll. Cardiol.* https://doi.org/10.1016/j.jacc.2024.03.387 (2024).
140. McDonagh, T. A. et al. 2023 focused update of the 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur. Heart J.* **44**, 3627–3639 (2023).
141. Lopaschuk, G. D. & Verma, S. Mechanisms of cardiovascular benefits of sodium glucose co-transporter 2 (SGLT2) inhibitors. *JACC Basic. Transl. Sci.* **5**, 632–644 (2020).
142. Subramanian, M. et al. Efficacy of SGLT2 inhibitors in patients with diabetes and nonobstructive hypertrophic cardiomyopathy. *Am. J. Cardiol.* **188**, 80–86 (2023).
143. Aglan, A. et al. Impact of sodium-glucose cotransporter 2 inhibitors on mortality in hypertrophic cardiomyopathy. *JACC Adv.* **3**, 100843 (2024).
144. Schoonvelde, S. A. C., Wiethoff, I., Hiligsmann, M., Evers, S. M. A. A. & Michels, M. Quality of life and societal costs in hypertrophic cardiomyopathy: protocol of the AFFECT-HCM study. *Neth. Heart J.* **31**, 238–243 (2023).
145. Nassif, M. et al. Validation of the Kansas city cardiomyopathy questionnaire in symptomatic obstructive hypertrophic cardiomyopathy. *JACC Heart Fail.* **10**, 531–539 (2022).
146. Spertus, J. A. et al. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): health status analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* **397**, 2467–2475 (2021).
147. Reaney, M. et al. Development of the hypertrophic cardiomyopathy symptom questionnaire (HCMSQ): a new patient-reported outcome (PRO) instrument. *PharmacoEconomics Open* https://doi.org/10.1007/s41669-022-00335-5 (2022).
148. Argiro, A. et al. Applications of gene therapy in cardiomyopathies. *JACC Heart Fail.* https://doi.org/10.1016/j.jchf.2023.09.015 (2023).
149. Hong, K. N. et al. International consensus on differential diagnosis and management of patients with danon disease. *J. Am. Coll. Cardiol.* **82**, 1628–1647 (2023).
150. Rossano, J. et al. Safety profile of the first pediatric cardiomyopathy gene therapy trial: RP-A501 (AAV9:LAMP2B) for danon disease. *J. Card. Fail.* **29**, 554 (2023).
151. Rocket pharmaceuticals announces positive updates from phase 1 clinical trial for RP-A501 in danon disease at the Heart Failure Society of America (HFSA) annual scientific meeting 2022.
152. Greenberg, B. et al. Phase 1 study of AAV9.LAMP2B gene therapy in danon disease. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa2412392 (2024).
153. Greer-Short, A. et al. AAV9-mediated MYBPC3 gene therapy with optimized expression cassette enhances cardiac function and survival in MYBPC3 cardiomyopathy models. *Nat. Commun.* **16**, 2196 (2025).
154. Haroldson, J. et al. MyPeak-1: a phase 1b study to evaluate safety and efficacy of TN-201, an adeno-associated virus serotype 9 (AAV9) investigational gene therapy, in adults with MYBPC3-associated hypertrophic cardiomyopathy (HCM). *J. Card. Fail.* **30**, S5 (2024).
155. Chai, A. C. et al. Base editing correction of hypertrophic cardiomyopathy in human cardiomyocytes and humanized mice. *Nat. Med.* **29**, 401–411 (2023).
156. Reichart, D. et al. Efficient in vivo genome editing prevents hypertrophic cardiomyopathy in mice. *Nat. Med.* **29**, 412–421 (2023).
157. Satish, T., Hong, K. N., Kaski, J. P. & Greenberg, B. H. Challenges in cardiomyopathy gene therapy clinical trial design. *JACC Heart Fail.* https://doi.org/10.1016/j.jchf.2024.08.024 (2024).
158. Xu, Z. et al. Incremental significance of myocardial oedema for prognosis in hypertrophic cardiomyopathy. *Eur. Heart J. Cardiovasc. Imaging* **24**, 876–884 (2023).
159. Wang, J. et al. Assessment of late gadolinium enhancement in hypertrophic cardiomyopathy improves risk stratification based on current guidelines. *Eur. Heart J.* **44**, 4781–4792 (2023).
160. Groarke, J. D. et al. Intrinsic mitral valve alterations in hypertrophic cardiomyopathy sarcomere mutation carriers. *Eur. Heart J. – Cardiovasc. Imaging* **19**, 1109–1116 (2018).
161. Nagueh, S. F. et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American society of echocardiography and the European association of cardiovascular imaging. *J. Am. Soc. Echocardiogr.* **29**, 277–314 (2016).
162. Gareri, C. et al. Antisense oligonucleotides and small interfering RNA for the treatment of dyslipidemias. *JCM* **11**, 3884 (2022).
163. Merino, J. L. et al. Practical compendium of antiarrhythmic drugs: a clinical consensus statement of the European heart rhythm association of the ESC. *Europace* https://doi.org/10.1093/europace/euaf076 (2025).
164. Ammirati, E. et al. Pharmacological treatment of hypertrophic cardiomyopathy: current practice and novel perspectives. *Eur. J. Heart Fail.* **18**, 1106–1118 (2016).

Author contributions

Introduction (I.O. and A.A.); Epidemiology (I.O., A.A. and V.P.); Mechanisms/pathophysiology (I.O., A.A. and V.P.); Diagnosis, screening and prevention (I.O., A.A., R.J., G.F., J.P.K. and E.A); Management (I.O., A.A., G.F., J.P.K. and E.A.); Quality of life (I.O. and A.A.); Outlook (I.O. and A.A.); overview of the Primer (I.O.).

Competing interests

A.A. is a consultant for Lexeo Therapeutics. I.O. is a consultant and/or adviser for Amicus Therapeutics, Inc.; Boston Scientific Corporation; Bristol Myers Squibb; Cytokinetics, Inc.; and Tenaya Therapeutics, Inc., and has received grant and/or research support from Amicus Therapeutics, Inc.; Bayer AG; Boston Scientific Corporation; Bristol Myers Squibb; Genzyme Corporation; The Menarini Group; Sanofi; Shire plc; and Takeda Pharmaceuticals International, Inc. E.A. is the Chief Science Officer for Lexeo Therapeutics, a shareholder with Rocket Pharmaceuticals and is a founder of Papillion Therapeutics and a founder, on the scientific board of and a shareholder of Corstasis Therapeutics. The other authors declare no competing interests.

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