



Hypertrophic cardiomyopathy: genetics and clinical perspectives

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Abstract: Hypertrophic cardiomyopathy (HCM) is the most common inherited heart disease and defined by unexplained isolated progressive myocardial hypertrophy, systolic and diastolic ventricular dysfunction, arrhythmias, sudden cardiac death and histopathologic changes, such as myocyte disarray and myocardial fibrosis. Mutations in genes encoding for proteins of the contractile apparatus of the cardiomyocyte, such as β -myosin heavy chain and myosin binding protein C, have been identified as cause of the disease. Disease is caused by altered biophysical properties of the cardiomyocyte, disturbed calcium handling, and abnormal cellular metabolism. Mutations in sarcomere genes can also activate other signaling pathways via transcriptional activation and can influence non-cardiac cells, such as fibroblasts. Additional environmental, genetic and epigenetic factors result in heterogeneous disease expression. The clinical course of the disease varies greatly with some patients presenting during childhood while others remain asymptomatic until late in life. Patients can present with either heart failure symptoms or the first symptom can be sudden death due to malignant ventricular arrhythmias. The morphological and pathological heterogeneity results in prognosis uncertainty and makes patient management challenging. Current standard therapeutic measures include the prevention of sudden death by prohibition of competitive sport participation and the implantation of cardioverter-defibrillators if indicated, as well as symptomatic heart failure therapies or cardiac transplantation. There exists no causal therapy for this monogenic autosomal-dominant inherited disorder, so that the focus of current management is on early identification of asymptomatic patients at risk through molecular diagnostic and clinical cascade screening of family members, optimal sudden death risk stratification, and timely initiation of preventative therapies to avoid disease progression to the irreversible adverse myocardial remodeling stage. Genetic diagnosis allowing identification of asymptomatic affected patients prior to clinical disease onset, new imaging technologies, and the establishment of international guidelines have optimized treatment and sudden death risk stratification lowering mortality dramatically within the last decade. However, a thorough understanding of underlying disease pathogenesis, regular clinical follow-up, family counseling, and preventative treatment is required to minimize morbidity and mortality of affected patients. This review summarizes current knowledge about molecular genetics and pathogenesis of HCM secondary to mutations in the sarcomere and provides an overview about current evidence and guidelines in clinical patient management. The overview will focus on clinical staging based on disease mechanism allowing timely initiation of preventative measures. An outlook about so far experimental treatments and potential for future therapies will be provided.

Keywords: Hypertrophic cardiomyopathy (HCM); molecular genetics; pathogenesis; clinical management; sudden cardiac death

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Prevalence and definition

Hypertrophic cardiomyopathy (HCM) is the most common inherited heart disease with a prevalence of 1/200 (1) to 1/500 (2).

The disease was first described as “Idiopathic subaortic stenosis” 60 years ago (3) and later classified as “hypertrophic cardiomyopathy” with or without left ventricular outflow tract (LVOT) obstruction based on functional and morphologic features by the European guidelines (4) and based on etiology by guidelines of the American Heart Association (5).

During the past two decades, mutations in genes that encode for proteins of the contractile apparatus of the cardiomyocyte have been identified as cause of the disease (6-8). Since then, over 450 mutations in 20 sarcomeric and myofibrillar-related proteins have been identified for HCM (5,7,9). However, most mutations affect genes encoding for the β -myosin heavy chain (*MYH7*) and myosin binding protein C (*MYBPC3*) of the cardiac sarcomere (9).

HCM is characterized by isolated progressive myocardial hypertrophy in the absence of another cardiac or systemic disease, typical histopathologic changes such as fibrosis and myocyte disarray, systolic and diastolic ventricular dysfunction, and arrhythmias (5,10). HCM is the number one reason for sudden cardiac death (11) in young adulthood (12,13) and in young athletes (14,15), but optimized risk stratification, prohibition of competitive sports, and the implantation of cardioverter-defibrillators

(ICD) has dramatically lowered mortality within the last decade (16).

With contemporary multidisciplinary and evidence-guided management life expectancy is usually relatively favorable (17-19). Approximately two thirds of patients with HCM experience a normal life span without significant morbidity (20,21). In the remaining patients, atrial fibrillation, heart failure and stroke contribute to morbidity later in life (13,22), requiring symptomatic heart failure therapies and heart transplantation (23,24).

Secondary causes of left ventricular hypertrophy (LVH), such as arterial hypertension, structural heart disease, or drug toxicity need to be ruled out before making the diagnosis of HCM. Other multisystem diseases, such as metabolic, endocrinologic, neuromuscular, neurologic, or autoimmune disorders and genetic syndromes can go along with typical features of HCM and need to be considered because management differs according to disease etiology (19,25-31) (*Table 1, Figure 1*). Those diseases should be termed disease-specific, such as Noonan cardiomyopathy or glycogen-storage cardiomyopathy to avoid confusion. The term “hypertrophic cardiomyopathy” or “HCM” should be used for disease secondary to mutations in the sarcomere or related structural proteins in the cardiomyocyte, or after careful exclusion of all systemic syndromes associated LVH mimicking HCM (10). The prevalence of HCM has become greater with the use of more sensitive imaging methods and the advance genetic testing allowing a molecular diagnosis prior to the onset of ventricular hypertrophy, which is an

Table 1 Differential diagnosis of left ventricular hypertrophy (LVH)

Disease	Gene	Protein	Phenotype	Work-up	OMIM #
Inborn errors of metabolism					
Glycogen storage cardiomyopathy	<i>PRKAG2</i>	γ -subunit AMP-activated protein kinase A	Severe myocardial hypertrophy, ventricular pre-excitation pattern	Molecular genetics, histopathology, CMR, ECG	600858
Pompe disease	<i>GAA</i>	α -1,4-glucosidase (acid maltase)	Age of onset in infancy, multiorgan disease, autosomal recessive, ventricular pre-excitation	Molecular genetics, histopathology, CMR, ECG, enzyme assay	232300
Anderson-Fabry disease	<i>GLA</i>	α -galactosidase A	Multisystem, involving skin, kidney, and peripheral nerves, X-linked inheritance	Molecular genetics, histopathology, CMR, enzyme assay, other organ involvement	301500
Danon disease	<i>LAMP2</i>	Lysosome-associated membrane protein 2	Muscle weakness, neurologic involvement, X-linked dominant, short PR on ECG, elevated CK levels	Molecular genetics, histopathology, CMR, other organ involvement	300257
Amyloidosis	<i>TTR</i>	Transthyretin	Other organ involvement	Molecular genetics, CMR	105210

Table 1 (continued)

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Disease	Gene	Protein	Phenotype	Work-up	OMIM #
Malformation syndromes/rasopathies					
Noonan syndrome, Noonan syndrome with multiple lentiginos (NS-ML)	<i>PTPN11</i> ; <i>RAF1</i> ; <i>RIT1</i> ; <i>SOS1</i> ; <i>others</i>	Protein tyrosine phosphatase nonreceptor type 11. Murine leukemia viral oncogene homolog 1. GTP-binding protein Rit1. Son of sevenless	Age of onset in infancy, craniofacial dysmorphologies, skin and hair involvement, other structural heart disease, biventricular involvement	Molecular genetics, other organ involvement	163950; 151100
Costello	<i>HRAS</i>	Transformin protein p21			218040
Cardiofaciocutaneous (CFC)	<i>BRAF</i>	B-Raf proto-oncogene, serine/threonine kinase			115150
Neuromuscular					
Friedreich Ataxia	<i>FRDA</i>	Frataxin	Neurodegeneration, autosomal recessive	Molecular genetics, other organ involvement	229300
Myotonic dystrophy	<i>DMPK</i>	Myotonin protein kinase	Myotonia, muscular dystrophy, cataracts, cardiac conduction system disease	Molecular genetics, ECG, other organ involvement	160900
Niemann-Pick disease	<i>NPC1</i>	Niemann-Pick	Neurodegenerative, autosomal recessive	Molecular genetics, other organ involvement	257220
Refsum disease	<i>PAHX</i>	Phytanoyl-CoA hydroxylase	Peripheral neuropathy, retinitis pigmentosa, ataxia	Molecular genetics, other organ involvement	266500
Mitochondrial					
Kearns-Sayre syndrome	<i>mtDNA</i>	Mitochondrial protein	Multisystem disease	Molecular genetics, other organ involvement	530000
MELAS	<i>mtDNA</i>	Mitochondrial protein	Multisystem disease	Molecular genetics, other organ involvement	540000
MERFF	<i>mtDNA</i>	Mitochondrial protein	Multisystem disease	Molecular genetics, other organ involvement	545000
Others (mutations in respiratory chains)	<i>Nuclear DNA</i> or <i>mtDNA</i>	Electron transport chain complex subunits and their assembly factors	Multisystem disease	Molecular genetics, other organ involvement	
Others					
Arterial hypertension			Arterial hypertension, renal involvement	Elevated blood pressure	
Athlete's heart			Concentric hypertrophy, enlarged ventricular cavity, no diastolic or systolic dysfunction, reversible	Classical features on TTE and ECG, no fibrosis on CMR, reversible after deconditioning	
Loading conditions (pressure or volume overload)			Structural heart disease	Transthoracic echocardiography	
Drug toxicity (e.g., anthracycline)					

Shown are the differential diagnosis of LVH; affected genes, corresponding proteins, disease-specific clinical findings, suggested clinical work-up, and the Online Mendelian Inheritance in Man (OMIM) reference. LVH can be the adaptive consequence to altered loading conditions, drug toxicity or with competitive exercise. Syndromic, neuromuscular and metabolic multisystem diseases are often associated with LVH. The diagnosis of hypertrophic cardiomyopathy (HCM) is made if LVH occurs isolated and if other causes are excluded. The differentiation between HCM and LVH in the setting of another disease is of crucial importance since management of patients and treatment are distinct depending on underlying etiology. CMR, cardiac magnetic resonance imaging; ECG, electrocardiogram; TTE, transthoracic echocardiography.

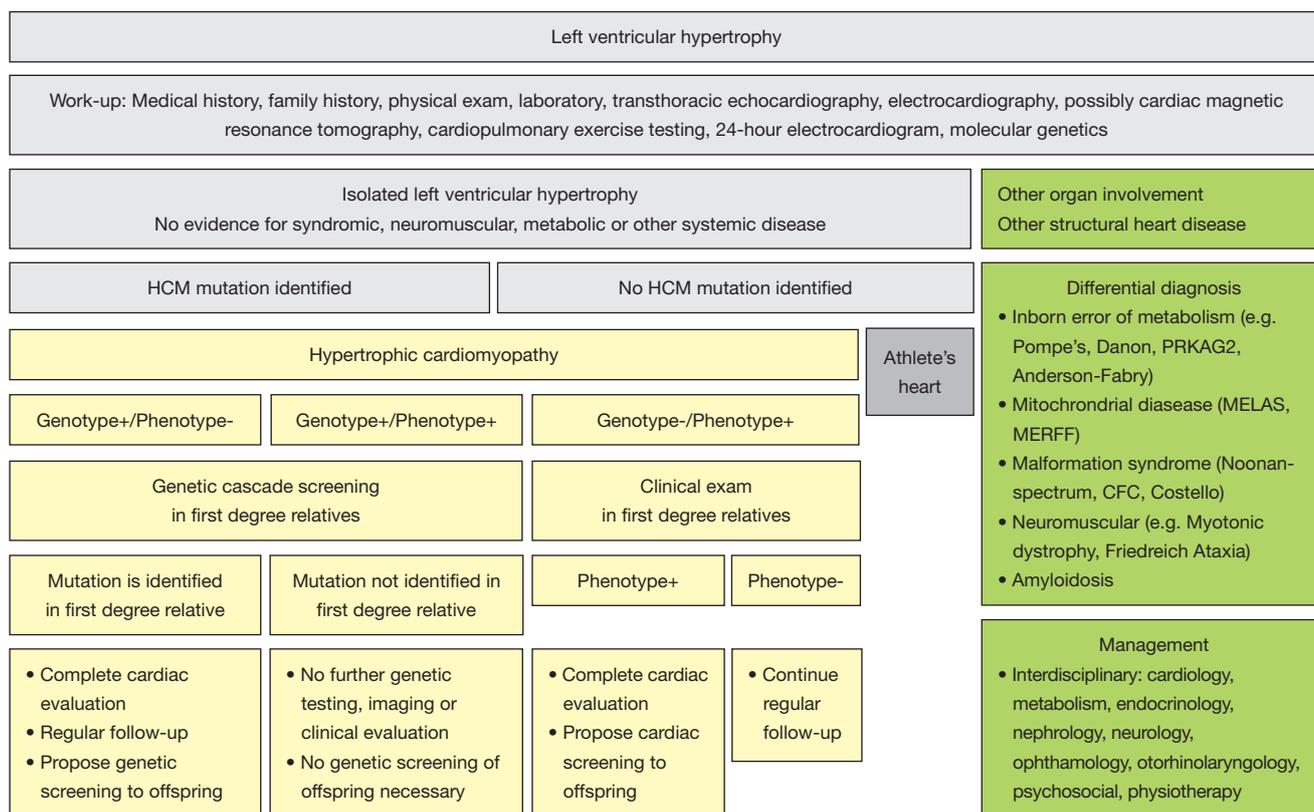


Figure 1 Differential diagnosis of unexplained left ventricular hypertrophy. Left ventricular hypertrophy (LVH) can present isolated or be associated with an underlying multisystem disorder. The diagram presents an overview of distinct etiologies causing LVH. The proposed clinical work-up applies for adult patients and is incorporated as class I and class IIA indications according to ESC (32) and AHA (18) guidelines. Establishing the correct diagnosis in a patient presenting with LVH is crucial to offer specific treatment and counseling. Genetic and clinical family screening is important if a diagnosis of hypertrophic cardiomyopathy (HCM) is made to identify asymptomatic disease carriers. ECG, electrocardiogram; TTE, transthoracic echocardiography; MELAS, mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes; MERFF, myoclonic epilepsy with ragged red fiber; CFC, cardiofaciocutaneous syndrome.

age-dependent process (1,2,33-35).

Pathogenesis

HCM is caused by mutations in sarcomere genes

The underlying genetic cause of HCM was described in the 1990 by identification of a sarcomere mutation in a large family presenting with HCM, sudden death, and heart failure (6,36). Since then, the report of multiple separate mutations in distinct sarcomere proteins (37), the regulators of contraction and relaxation of the heart, established HCM as a genetically heterogeneous disease. Among the known causal genes, *MYH7* and *MYBPC* are the two most common (38,39) followed by mutations in *TNNT2* and *TNNI3* (40,41). Rarely reported are mutations in genes encoding

for other components of the sarcomere (42) (Table 2).

Disease variability in HCM

Carrying a heterozygous sarcomere gene mutation alone cannot fully explain HCM pathology as the clinical course of the disease varies greatly with variable expressivity (8), age penetrance, and a high clinical heterogeneity, even within patients or family members carrying the same mutation (43-46) or within genetically engineered identical mice (47).

Thus, the primary defect is the sarcomere mutation, but clinical expression is determined by a complex hierarchy of genetic, epigenetic, and environmental factors (Figure 2).

In the past decades, basic science and research on

Table 2 Genes associated with sarcomere hypertrophic cardiomyopathy

Gene	Sarcomere protein	OMIM #	Frequency (%)
Thick myofilament			
<i>MYBPC3</i>	Myosin binding protein C	600958	~40
<i>MYH7</i>	β -myosin heavy chain	160760	~40
<i>MYL2</i>	Myosin light chain 2	160781	<1
<i>MYL3</i>	Myosin light chain 3	160790	<1
Thin myofilament			
<i>ACTC1</i>	Cardiac α -actin	102540	<1
<i>TNNC1</i>	Cardiac troponin C	191040	<1
<i>TNNI3</i>	Cardiac troponin I	191044	<5
<i>TNNT2</i>	Cardiac troponin T2	191045	~10
<i>TPM1</i>	α -tropomyosin	191010	<1
Z-disc			
<i>ACTN2</i>	α -2 actinin	102573	<1
<i>CSRP3</i>	Cysteine and glycine-rich protein 3	600824	<1
<i>MYOZ2</i>	Myozenin 2	605602	<1
<i>TCAP</i>	Telethonin	604488	<1
<i>TTN</i>	Titin	188840	<1

Shown are genes which are affected in hypertrophic cardiomyopathy (HCM), the corresponding protein, and Online Mendelian Inheritance in Man (OMIM) reference. The genetic yield of a molecular diagnostic test in patients is currently about 60%. Percentages shown are of all patients with a positive genetic finding. Patients with HCM most commonly test positive for mutations in myosin binding protein C (*MYBPC3*) and in β -myosin heavy chain (*MYH7*).

genetically modulated animal models (48), human tissue (49) and human induced pluripotent cell models (50) contributed to our understanding of disease.

First, mutations directly alter the structure and function of the sarcomere proteins and alter biophysical properties of the cardiomyocyte (51-56), influence calcium handling (57), and change cellular energy balance (58-61). Additionally, mutations can directly initiate other signaling pathways via transcriptional activation (62,63); including expression and activation of trophic and mitotic factors, such as calcineurin, mitogen-activated protein kinases, and transforming growth factor beta pathways (64-67) and stimulate non-cardiac cells, such as fibroblasts (68). Genetic variants in signaling pathways implicated in regulating cardiac hypertrophy and fibrosis can influence expression of the HCM phenotype and function as modified genetic variants. Hence, modifier variants due to distinct genetic background can in part, explain interindividual variability in the phenotypic expression of HCM (69).

In addition to direct effects of the underlying sarcomere mutation, secondary molecular and intracellular changes occur in response to the changes of sarcomere protein structure and function. Those include epigenetic modifications and posttranslational modifications, such as micro RNAs (miRNAs), small noncoding RNAs with 22 nucleotides, regulating gene expression at the posttranscriptional level (70,71) and histone modifications (57,65,68,72).

The primary and secondary effects of the mutations ultimately lead to the functional pathological phenotypes, such as myocardial hypertrophy and ventricular dysfunction. The interplay of microvascular ischemia, cardiomyocyte energy depletion and apoptosis, leads to adverse remodeling with progressive myocyte loss and fibrous substitution of the myocardium, presenting as the histological phenotypes of myocyte disarray and myocardial fibrosis (60,73-75). The same pathomechanisms that cause adverse remodeling ultimately lead to the irreversible stage of overt dysfunction

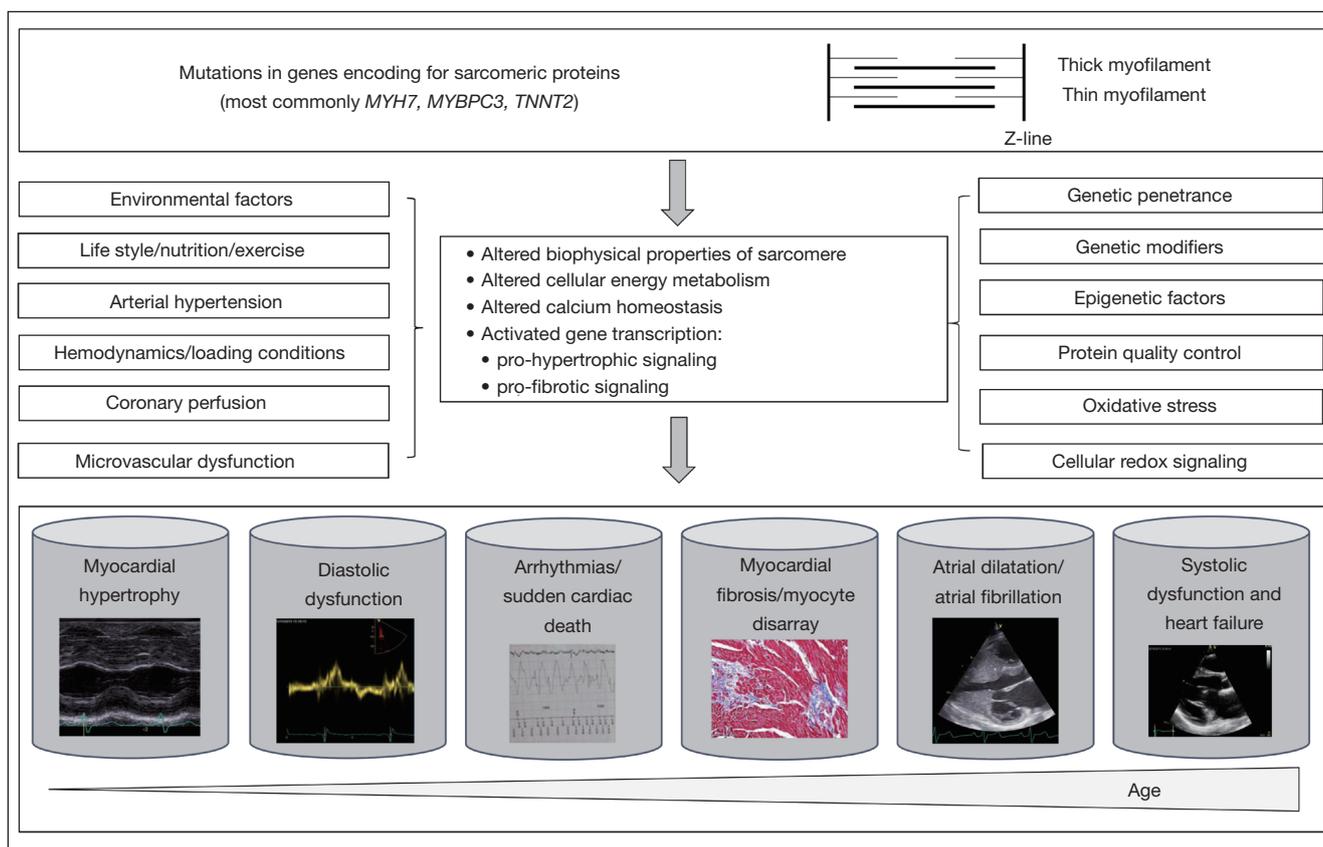


Figure 2 Pathogenesis of hypertrophic cardiomyopathy. The primary defect is the mutation in a gene encoding for a sarcomere protein. This mutation alters protein expression, morphology and function and influences sarcomere assembly, force generation, intracellular calcium homeostasis, and ATPase activity. Those altered biophysical and intracellular properties cause cardiomyocyte hypertrophy, diastolic and systolic dysfunction, rhythm disturbances and histopathologic changes over time. The underlying gene defect initiates secondary molecular changes, such as pro-hypertrophic and pro-fibrotic signaling (e.g., TGF- β , Periostin, MEF2, MAPK, RAS, NFAT), gene expression, post-translational modifications, mitochondrial dysfunction and mitotic factors. Those changes lead to the pathognomic histopathological changes, such as myocyte disarray and myocardial fibrosis. Arrhythmias can occur as a sequela of both disturbed intracellular calcium handling, cardiomyocyte hypertrophy and myocardial histopathological changes. Other pathogenic genetic variants (modifiers), genomic/epigenetic factors (e.g., miRNA, long non-coding RNA, histon modification), proteomics (e.g., post-translational modifications, cell-cell-communication) and environmental factors contributing to expression of the phenotype and result in large clinical variability.

and ultimately severe heart failure and death (76,77).

Arrhythmias in HCM are caused by both the primary mutation effects, such as disturbed calcium handling causing triggered activity by electrical afterdepolarization (78), as well as the secondary effects, such as cardiomyocyte hypertrophy increasing myocyte automaticity (79) and myocardial fibrosis creating reentry (80-83) (Figure 3). Transient pathophysiological factors, such as maladaptive autonomic responses, myocardial ischemia, and altered hemodynamics (81,84), influence arrhythmogenicity in HCM.

Clinical disease stages and underlying myocardial pathology

The pathogenic HCM mutation initiates a life-long remodeling process within the myocardium which presents with distinct clinical disease stages (60,85,86). Initially, there is the “non-hypertrophic HCM” which is characterized by the absence of LV hypertrophy in individuals harboring HCM-causing mutations, investigated during systemic family screening (stage 0, Figure 4). The prevalence of

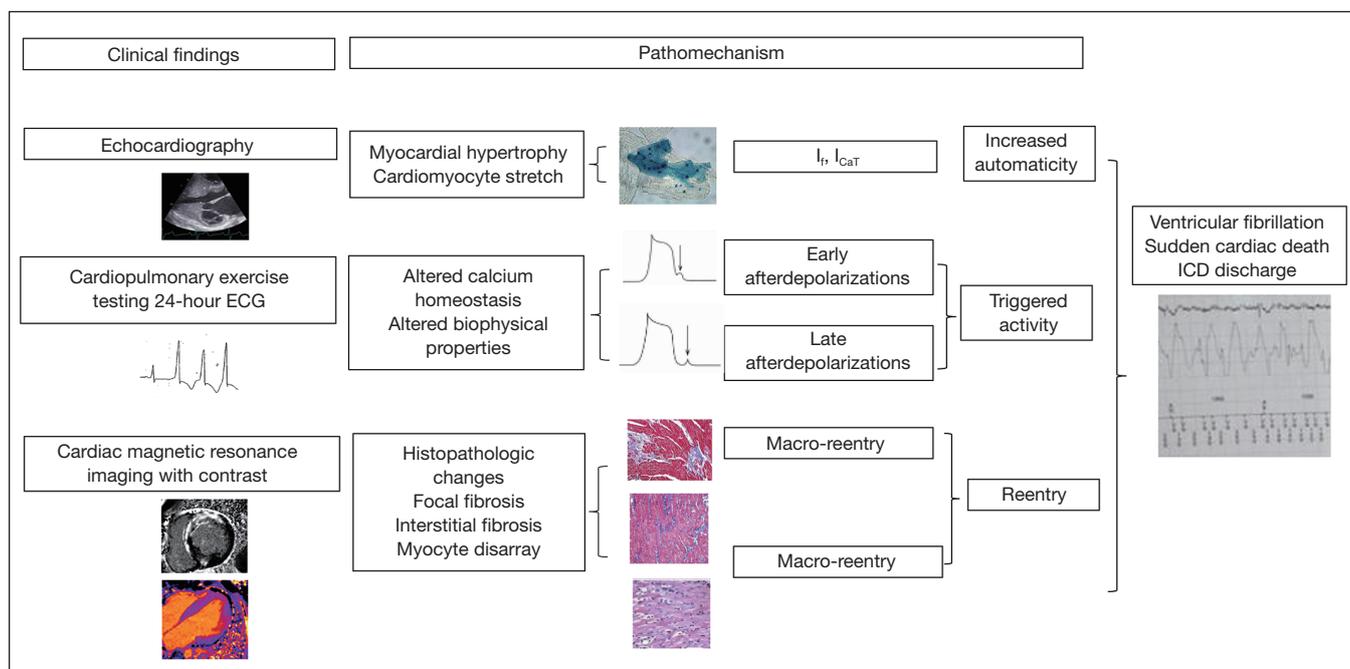


Figure 3 Pathomechanisms and associated clinical findings of arrhythmias in hypertrophic cardiomyopathy. Abnormal automaticity, triggered activity, and reentry promote ventricular arrhythmia which can ultimately cause sudden cardiac death. In hypertrophic cardiomyopathy, cardiomyocyte stretch is believed to increase automaticity by influencing self-depolarizing channels, such as the funny channel I_f and the T-type calcium channel I_{CaT} . Altered calcium homeostasis and altered biophysical properties can initiate early and late afterdepolarizations, presenting as premature ventricular contractions on Holter monitoring, which in turn can initiate non-sustained and sustained ventricular arrhythmias. Myocyte disarray, focal and interstitial fibrosis provide the anatomical substrate that predisposes to conduction block and promote macro- and microreentry arrhythmias. Multiple transient pathophysiological factors, such as altered hemodynamics, autonomic responses, or myocardial ischemia modulate the arrhythmogenic potential favoring electrical triggers.

patients in this stage has increased given incorporation of systemic family screening and molecular testing and is estimated at about 0.6% (1:167) (1). Individuals in this stage are defined as “genotype-positive/phenotype-negative” (Genotype +/Phenotype-). Medical notes should describe such patients’ diagnosis as “pre-clinical hypertrophic cardiomyopathy”, or “hypertrophic cardiomyopathy without clinical signs”.

Stage I

Stage I of the disease is defined by the development of LVH with or without LVOT obstruction, hyperdynamic ventricular function, and mild symptoms, such as decreased exercise tolerance or intermittent chest pain. Arrhythmias can occur during this stage (stage I, *Figure 4*). Onset of this stage occurs in approximately one half of patients by the third decade of life and in about three fourths

by the sixth decade (59,60,85,87). Subtle abnormalities on electrocardiogram (ECG) or on transthoracic echocardiography (TTE), such as impaired LV relaxation, mitral valve abnormalities or mild left atrial dilatation might be present during this stage. Elevated levels of type I collagen precursors (88) and altered coronary microvascular function (74) have been described in this stage. Counseling regarding prognosis in this stage is challenging with current methodologies. Risk for sudden cardiac death is generally low, but potentially malignant arrhythmias can occur, specifically in patients harboring a mutation in the cardiac troponin T gene (89).

Stage II

Adverse myocardial remodeling with increasing myocardial hypertrophy and fibrotic changes occurs during stage II of the disease (stage II, *Figure 4*). The prevalence of this

	Disease stage	Clinical findings	Management
Age (variable disease progression)	Genotype + / Phenotype -		
	Stage 0 <ul style="list-style-type: none"> • Mutation carrier • No clinical phenotype 	<ul style="list-style-type: none"> • Asymptomatic 	<ul style="list-style-type: none"> • Regular cardiac evaluation (every 1 to 2 years before 20 years of age, every 2 to 5 years after 20 years of age) • Family counseling and screening
	Genotype - or + / Phenotype +		
	Stage I <ul style="list-style-type: none"> • Isolated left ventricular hypertrophy with or without left ventricular outflow tract obstruction 	<ul style="list-style-type: none"> • No or mild symptoms • No or mild diastolic dysfunction • Hyperdynamic function • With and without arrhythmias 	<ul style="list-style-type: none"> • Regular cardiac evaluation • Treat left ventricular outflow tract obstruction • Sudden death risk stratification • Identify progression to stage II
	Stage II <ul style="list-style-type: none"> • Adverse remodeling: progressive hypertrophy and histopathologic changes (fibrosis) 	<ul style="list-style-type: none"> • Diastolic dysfunction • Left atrial enlargement • Positive late gadolinium enhancement and / or increased T1 map on CMR • Fibrosis on histopathology 	<ul style="list-style-type: none"> • ICD implantation for primary or secondary prevention • Treat atrial fibrillation • Treat diastolic dysfunction • Pharmacologic prevention of disease progression
Stage III <ul style="list-style-type: none"> • Overt dysfunction = "end-stage" 	<ul style="list-style-type: none"> • Severe systolic and diastolic dysfunction • Heart failure • Arrhythmias 	<ul style="list-style-type: none"> • Heart failure therapy • ICD implantation • Left ventricular assist device • Heart transplantation 	

Figure 4 Clinical disease stages and stage-specific clinical management of hypertrophic cardiomyopathy. Hypertrophic cardiomyopathy (HCM) is a congenital heart defect, but disease progression occurs over life and medical management needs to be adopted to disease stage. Molecular testing can diagnose the underlying genetic defect before the disease becomes overt in a patient (Genotype+/Phenotype-, stage 0, green boxes). Regular cardiac evaluation and appropriate family counseling needs to be performed during this stage. The frequency of cardiac screening should be based on family history, current guidelines, and healthcare provider recommendation. Stage I presents with myocardial hypertrophy in asymptomatic or mildly symptomatic patients with subtle clinical findings (yellow boxes). Treatment of left ventricular outflow tract obstruction and thorough risk stratification for sudden arrhythmic death is required during this stage. Regular cardiac evaluation should be performed to timely identify progression to the “adverse remodeling” stage (stage II, orange boxes). More aggressive treatment is typically required during this stage. Specific emphasis should be made on new therapeutic options preventing disease progression to avoid progression to end-stage disease (stage III, red boxes). Stage III presents usually an irreversible disease process in highly symptomatic patients. There is high morbidity and mortality during this stage.

stage is estimated at about 15% (85). Increasing LV fibrosis and worsening function with relatively preserved clinical and hemodynamic balance occurs during this stage. The extent and the time-course of LV remodeling are extremely heterogeneous (90). The clinical findings in this stage are a low to normal range LV ejection fraction (91), moderate to severe diastolic dysfunction (92), atrial dilatation (93), areas of late gadolinium enhancement (91), microvascular dysfunction (74), thinning of LV walls (94), onset of atrial fibrillation (95), and LV apical aneurysms (96). The clinical correlates of adverse remodeling may vary widely, ranging from mild to severe manifestations. Congestive symptoms

may become evident by impairment of cardiopulmonary exercise testing (CPET) and elevated titers of natriuretic peptides (97).

Stage III

Stage III presents then the irreversible “end-stage” of disease with high morbidity and mortality. The stage is characterized by extreme degrees of LV fibrosis, progression to LV dilatation, atrial dilatation, and systolic and diastolic dysfunction associated with hemodynamic decompensation, heart failure-related complications, heart transplantation

or death (90,98). A small number of HCM patients (<5%) progress to this end-stage phase of HCM (85,99). The stage can be differentiated between the so called “hypokinetic-dilated” form, characterized by a decrease in left ventricular wall thickness while end-diastolic cavity dimensions increases and ventricular function deteriorates (94), and the so called “hypokinetic-restrictive” form, characterized by a small and stiff LV with extreme diastolic dysfunction, resembling primary restrictive cardiomyopathy. In this form, systolic function is only mildly or moderately impaired, but marked bilateral atrial dilatation and atrial fibrillation are usually present (100). This form has been associated with mutations in thin filaments (101) but also occurs with other sarcomere mutations.

The extent and the rate at which each of these features occur and evolve are very variable determining clinical heterogeneity. In most of the patients, disease onset occurs between 20 and 50 years of age (22), but some patients also present during childhood (102), while others remain asymptomatic until late in life (85,103).

Clinical work-up

Once the suspicion of HCM has been made, or once a family member has been diagnosed with HCM, specific work-up is required for the presenting individual (*Figure 1*). Thorough clinical work-up including a detailed medical and family history, general and focused physical examination, electrophysiological assessment by electrocardiogram (ECG), 24-hour ECG, CPET, imaging by transthoracic echocardiography (TTE) and cardiovascular magnetic resonance imaging (CMR), as well as general and molecular genetic testing (*Table 3*) is required to exclude concomitant conditions that may mimic HCM (*Table 1*) and to appropriately stage HCM (*Figure 4*).

Importance of medical and family history

Despite the presence of cardiac hypertrophy, patients with HCM are commonly asymptomatic or minimally symptomatic. Often HCM is diagnosed in asymptomatic patients by the incidental finding of a murmur or by a family member being diagnosed with HCM and prompting family evaluation. Approximately 60% of patients with HCM have a clearly recognizable familial disease (107). A detailed family history and generation of a family tree (108) is helpful in evaluating phenocopy conditions mimicking HCM (109), inheritance pattern and malignancy of HCM

phenotype, and identifying other family members at risk (110-114) (*Figure 5*). In HCM there is usually an autosomal dominant pattern of inheritance (115).

Assessment of arrhythmias and electrocardiographic parameters

Rhythm disturbances in HCM include the occurrence of supraventricular and ventricular ectopic beats, and rarely with non-sustained or sustained ventricular tachycardia (116-118). Atrial fibrillation occurs in patients with advanced clinical stage or severe LVOT obstruction (119,120) and is a major risk factor for heart failure (95) and for thromboembolic stroke (121). Left atrial size and function as well as LVOT obstruction are major risk factors for atrial fibrillation.

Arrhythmias can be detected by ECG, 24-hour ECG (122), or CPET (123).

In general, ECG is abnormal in most patients with HCM and may show voltage changes of LVH, ST-T wave changes, T-wave inversions, pathological deep Q waves caused by depolarization of a hypertrophied interventricular septum, complete bundle branch block and evidence of left atrial enlargement (124). Extremely high-voltage QRS complexes or a delta-wave should raise the possibility of a phenocopy condition mimicking HCM. Common ECG patterns in athletes might include sinus bradycardia, sinus arrhythmia, J-point elevation with ascending ST-segments, first degree atrioventricular block, and incomplete right bundle branch block (125). Peak oxygen consumption on CPET can help to differentiate between athlete's heart and HCM, being high in athletes and low in HCM.

Imaging in HCM

Imaging in HCM is imperative to establish the diagnosis, risk stratification, and disease monitoring of patients (126,127).

Echocardiographic examination by TTE is the primary imaging modality used in evaluation of a patient to exclude structural heart disease, and to assess myocardial morphology and function.

LVH on TTE in an adult is defined by a wall thickness of equal or greater than 15 mm in one or more left ventricular myocardial segments and equal or greater than 13 mm in first-degree relatives of HCM patients (2,4,32) (*Figure 5*). In children, cardiac hypertrophy is defined by z-scores above 2 of the age- and sex-matched population (128).

Table 3 Clinical work-up of a patient with unexplained left ventricular hypertrophy

Diagnostic work-up	Category	Details
History	Medical history	General history: neuromuscular development, growth, vision, hearing, seizures, other organ involvement Cardiac history: age of onset, disease progression, heart failure, chest pain, syncope, palpitations, dizziness, nausea, exercise tolerance
	Family history	Cardiomyopathies, sudden deaths, fetal loss, family members with recurrent syncope, chest pain, exercise intolerance, palpitations, implantable cardioverter-defibrillator, dysmorphologies, multisystem diseases
Physical exam	General	Dysmorphologies, muscle involvement, other organ involvement
	Cardiac	Murmurs/gallop/rub, rhythm, perfusion, auscultation at rest and after provocation (left ventricular outflow tract obstruction?), signs of heart failure
Electrophysiology	Electrocardiogram	Signs of hypertrophy and ischemia, rhythm disorder, conduction system disease, assessment of intervals
	24-hour electrocardiogram	Arrhythmias
	Cardiopulmonary exercise testing	Arrhythmias
Imaging	Chest X-ray	Anatomy, congestion, effusions, other causes
	Transthoracic echocardiography	Anatomy, chamber sizes, ventricular diastolic and systolic function, location and grade of myocardial hypertrophy, outflow tract obstruction, systolic motion of the anterior mitral valve
	Cardiovascular magnetic resonance imaging with contrast	Anatomy, signs of inflammation, storage disease, fibrosis, aneurysm, myocardial crypts
Laboratory	General	Blood count, electrolytes, renal function, liver function, thyroid function, NT-proBNP
	Metabolic/mitochondrial	Blood gas analysis, lactate, pyruvate, urine organic acids, serum amino acids, acylcarnitine profile, glucosaminoglucones, creatine phosphokinase, specific enzyme testing, e.g., Fabry, Pompe, Danon or other metabolic diseases
	Molecular genetics	Cardiomyopathy panel or gene panel according to phenotype, whole exome analysis
Diagnostic cardiac catheterization and endomyocardial biopsy	Light microscopy	Myocyte disarray, myocardial fibrosis, specific staining for suspected metabolic disease or amyloidosis
	Electron microscopy	Suspected metabolic disease
	Others	Polymerase chain reaction for suspected myocarditis Specific enzyme assays in suspected metabolic disease

Shown is the suggested clinical work-up of a patient presenting with unexplained left ventricular hypertrophy (LVH) to exclude other causes for LVH and to diagnose HCM. Please refer to textbooks for further details. In general, low-cost diagnostic tests should be prioritized, costly diagnostic tests should only be performed in consideration of specific differential diagnosis based on medical history, family history, and physical exam. Modified and summarized from German (104), European (105) and North-American (106) guidelines.

Hypertrophy in HCM is commonly asymmetrical with the most severe hypertrophy involving the basal interventricular septum (129). Occasionally, myocardial hypertrophy is restricted to other myocardial regions, such as the apex, the midportion, and the posterior wall of

the left ventricle (130). Extreme ventricular hypertrophy or the involvement of the right ventricle should prompt the possibility of a phenocopy condition mimicking HCM, although rarely the right ventricle can be involved in HCM (85,131). Physiological cardiac hypertrophy

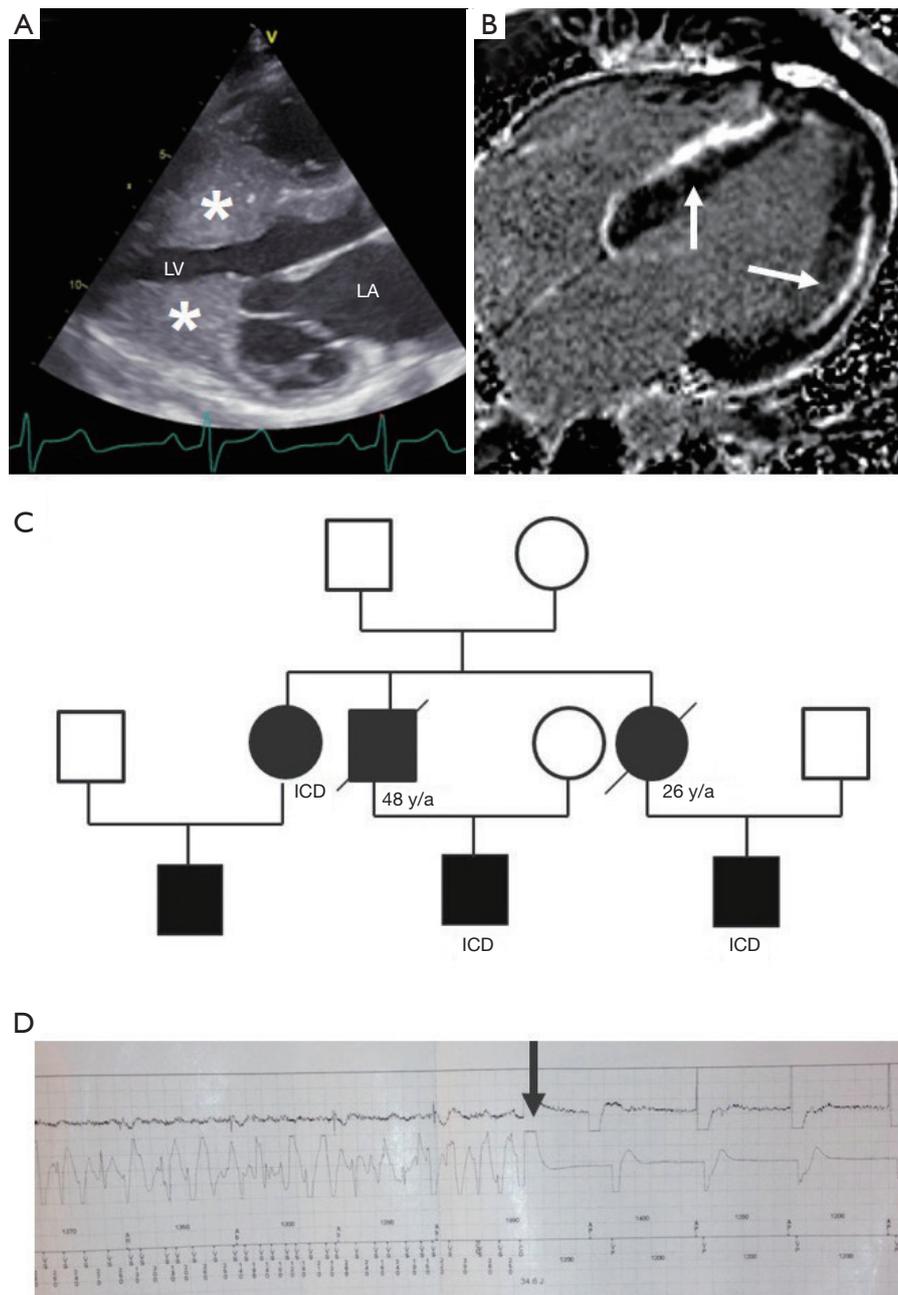


Figure 5 Typical clinical findings of patients with hypertrophic cardiomyopathy. Left ventricular (LV) hypertrophy (white stars) and left atrial (LA) enlargement can be best detected by transthoracic echocardiography (panel A). Focal myocardial fibrosis is diagnosed by positive late gadolinium enhancement (white arrows) on cardiac magnetic resonance tomography (panel B). Panel C: high incidence of sudden cardiac death or appropriate discharge of the implantable cardioverter defibrillator (ICD, black arrow on intracardiac electrogram panel D) in a family carrying a mutation in the β -myosin heavy chain (*MYH7*) and the cardiac troponin T (*TNNT2*) gene (black filled symbols, panel C).

in adolescents and adults who are active in competitive sports exhibits with left ventricular wall thickness between 13 and 18 mm (132). A distinguishing feature is

a symmetrical enlargement of all cardiac chambers (133), and the size of the left ventricular cavity, which is not enlarged in HCM, but is typically enlarged in the

physiological hypertrophy of the athlete's heart (134,135). In addition, the distribution pattern of cardiac hypertrophy with asymmetrical septal hypertrophy strongly favors HCM (136). The electrical and structural changes in athletes are considered benign and generally reversible after detraining.

Left ventricular outflow tract obstruction is present at rest or provoked in about two thirds of patients with HCM (21,25,107,137,138). Systolic anterior motion of the anterior mitral valve (SAM) might contribute to LVOT obstruction (3). Other frequent pathological features include elongation of the anterior or both leaflets of the mitral valve, as well as abnormal insertion of the associated papillary muscles (139).

Diastolic dysfunction in HCM is frequently detected by atrial enlargement and by abnormal pulsed Doppler tissue imaging on TTE (121,140-142).

Ejection fraction is elevated during the first clinical stages and reduced in end-stage HCM.

CMR is often necessary to exclude phenocopy conditions, such as Anderson-Fabry disease, amyloidosis, or other storage diseases (143). Additionally, morphological abnormalities, including myocardial crypts, left ventricular aneurysms or focal myocardial hypertrophy can be detected best by CMR (1,129,144,145). Focal fibrotic changes are detected by positive late gadolinium enhancement (2,88,146-148) (*Figure 5*) and interstitial fibrosis by increased extracellular volume fraction on CMR T1 map (149). Contrast CMR can help in identifying patients that transition from clinical stages I to clinical stage II of adverse remodeling (91), but the advisable frequency of scans during follow-up remains to be determined (18).

Other more advanced imaging technologies, such as CMR diffusion tensor imaging to assess myofibrillar orientation (150,151), single-photon emission computed tomography (PET) (127), or the use of speckle tracking and strain imaging on echocardiography and CMR (152-156) are under investigation but not in routine clinical use yet.

Laboratory and molecular genetic testing

General laboratory examination and specific metabolic testing, such as enzyme-assays to detect specific glycogen or lysosomal storage disorders, needs to be undertaken to exclude phenocopy conditions mimicking HCM (157).

Molecular testing has now become a powerful diagnostic aid in routine cardiovascular practice through commercially available DNA-based testing for disease-causing mutations

(158,159) and can help to diagnose both HCM as well as phenocopy conditions (*Table 1*).

Genetic testing is a class I indication in both the European as well as the North-American guidelines (32,106,107,160). Molecular genetic testing is indicated in patients with clinical signs and symptoms for HCM suggestive of HCM to confirm diagnosis, in patients fulfilling HCM diagnosis to enable genetic cascade screening in relatives, and in first degree relatives with definite disease-causing mutations after pre-test counseling (*Figure 1*).

Genetic testing, when positive, will support the diagnosis in a patient, but if it is negative, it will not exclude it.

The majority of genes and mutations, which are responsible for clinically diagnosed HCM, encode proteins of the sarcomere (6,19,161) (*Table 2*). Of those, *MYH7* and *MYBPC3*, encoding β -myosin heavy chain and myosin-binding protein C, respectively, are the two most common genes involved, together accounting for about 50% of the HCM families. In about 40% of HCM patients, the causal genes remain to be identified (32,106,107,162).

Criteria for assessing variant pathogenicity are based on the variant type, variant database, literature review, frequency in the general population, and *in silico* analysis, meaning the influence of the genetic variant on protein morphology and function (163,164). However, interpretation of the findings in molecular genetic testing can be extremely challenging. Each human genome contains an average of about 11,000 nonsynonymous variants, 160 premature protein truncation variants, and 500,000 variants in the known regulatory regions (165). Given variability of phenotypic expression of HCM there is often uncertain evidence of causality for many mutations possibly implicated in HCM (39,42). This can result in reclassification of variants (166,167).

Cardiac catheterization and endomyocardial biopsy

Given modern imaging modalities and molecular genetic testing as well as enzyme testing, cardiac catheterization and endomyocardial biopsy is not performed in the first line of diagnosis in a patient presenting with LVH. However, in unresolved or unclear conditions, endomyocardial biopsy and specific histological examination may identify phenocopy conditions mimicking HCM, such as glycogen-filled cardiomyocytes in glycogen-storage cardiomyopathy (157) or amyloid depositions in amyloidosis (168). In HCM, histopathology of endomyocardial biopsy specimens with

identify enlarged cardiac myocytes that present in disarray with loss of normal parallel alignment giving a swirling appearance to the myocardial architecture (169-171). Additionally, focal and interstitial fibrotic replacement of the myocardium on histopathology is pathognomic for HCM (9).

Management

Phenocopy conditions mimicking HCM need to be diagnosed in time because of the possibility of medical treatment and cure in a subset of those diseases by enzyme replacement therapies specifically in Anderson-Fabry (26-29) and in Pompe's disease (30) or by supportive therapies (e.g., Co-enzyme Q10 in mitochondriopathies) (31).

No causal therapy is available for HCM, so that the focus of current management is on early identification of asymptomatic patients at risk through molecular diagnostic and clinical cascade screening of family members, optimal sudden death risk stratification, and timely initiation of preventative therapies (94,172) to avoid disease progression to the irreversible adverse myocardial remodeling stage (17,76) (*Figure 4*).

During stage 0 of disease, there is a focus on appropriate counseling of patients and families about the disease pathogenesis and basic understanding of the genetic and molecular basis of the disease should be done during this stage. This is of importance, since asymptomatic patients might otherwise be lost to follow-up and suffer from sudden arrhythmic death or advance to the severe adverse remodeling stage without timely prevention strategies. If not already done, patients should also be referred to specialized centers with interdisciplinary teams consisting of cardiologist, pediatric cardiologist and human geneticist (173).

Relief of LVOT obstruction (19), avoiding competitive sports and risk stratification for sudden death is the mainstay of therapy during stage I of the disease. Control of conventional risk factors such as sedentary lifestyle, hypertension, dyslipidemia, and diabetes (174), and regular clinical follow-ups to timely identify progression to stage II are necessary during stage I (*Figure 4, Table 4*).

HCM patients in stage II with adverse cardiac remodeling are considered at risk of further progression toward overt dysfunction and need close clinical surveillance with CMR, CPET, serial NT-proBNP assessment to allow for preventive treatment (190). The decline in LV function and progression of symptoms may be slow and patients can be stabilized for years by heart failure treatment (18,19,59).

Patients with the hypokinetic-restrictive subtype are more challenging to manage as they do not tolerate or benefit from standard heart failure therapies. In those patients it is crucial to avoid missing a window for transplant listing (98). Aggressive treatment of atrial fibrillation might play a role during this stage to prevent functional and clinical deterioration in HCM patients (95).

Management of overt dysfunction in stage III is based on standard guidelines for heart failure (18) (*Figure 4, Table 4*). Commonly accepted measures include ACE inhibitors and angiotensin receptor blockers, heart-failure specific β -blockers, spironolactone, loop diuretics, and, in the presence of atrial fibrillation or an apical aneurysm, oral anticoagulants for cardioembolic prevention (18,19,86,90,95). In addition, overt dysfunction should be considered as potential indication for primary arrhythmic death and implantable cardioverter-defibrillator (ICD) implantation (90). Resynchronization by biventricular pacing may represent a promising option for the improvement of LV efficiency and symptoms in HCM patients with overt dysfunction (191). Tailored surgical options may present in individual cases, such as mitral plasty to correct annulus dilation and regurgitation, implantation of an left ventricular assist device, and cardiac transplantation (77,98).

Family evaluation

Evaluation of family members by clinical and molecular genetic screening is a class I indication in both the European and North-American guidelines (32,106,107,160) (*Figure 1*). If a disease-causing mutation has been identified, specific genetic testing can be performed in offspring (104,106). If no mutation has been identified, clinical examination needs to be undertaken every 3 to 5 years before 10 years of age, every 1 to 2 years between 10 and 20 years of age, and every 2 to 5 years after 20 years of age since HCM has an age-dependent disease onset and disease cannot be excluded until later in life (45,160).

Prevention and sudden death risk stratification

Given the high risk for sudden cardiac death in competitive athletes (14,15) and the possibility of disease acceleration with exercise (48,192,193), European and North-American guidelines do not recommend the participation in competitive sports for patients with clinically overt HCM (stage I and above) (32,194). There is an ongoing debate

Table 4 Therapeutic options in hypertrophic cardiomyopathy

Treatment	Comment	Literature/clinical trials
Left ventricular outflow tract obstruction		
Pharmacologic	Cave: obstructive airway disease, bradycardia	(18,19,32). Ongoing trial: NCT03532802 (TEMPO)
β-blocker	Titrate to effect, cave: heart rate variability	(175)
High-dose β-blocker	IA antiarrhythmic, negative inotropy; cave: QTc prolongation	(18,19,32,176)
Disopyramide		
Invasive		
Percutaneous transluminal septal myocardial ablation	Highly operator dependent; cave: atrioventricular block	(18,19,32,177,178)
Operative septal myectomy (Morrow-procedure)	Operator and center-dependent	
Diastolic dysfunction		
Pharmacologic		
β-blocker	Negative inotropy, increased ventricular relaxation, increased diastolic filling; cave: obstructive airway disease, bradycardia	(18,19,32)
Diltiazem	Negative inotropy and chronotropy, increased ventricular relaxation, increased diastolic filling; cave: atrioventricular block, left ventricular outflow tract obstruction; contraindicated in infants and children	
High risk malignant arrhythmias		
Invasive		
ICD	Indication according evidence-based risk stratification	(18,19,32)
Atrial fibrillation		
Pharmacologic		
Anticoagulation		(18,19,32)
Rate control (β-blocker, Verapamil, Diltiazem, Digoxin)		
Rhythm control (Amiodarone, Disopyramide)		
Invasive		
Electrical cardioversion		
Radiofrequency ablation		
Maze procedure		
Atrioventricular node ablation and pacemaker placement		

Table 4 (continued)

Table 4 (continued)

Treatment	Comment	Literature/clinical trials
Systolic dysfunction/heart failure		
Pharmacologic		
Afterload reduction	Cave: left ventricular outflow tract obstruction	(18,19,32)
Beta-blocker		
Diuretics	Cave: left ventricular outflow tract obstruction	
Spironolactone	Cave: hyperkalemia	
Angiotensin receptor blocker		
Invasive		
Left ventricular assist device		
Heart transplantation		
ICD		
Prevention of progressive pathologic remodeling		
Pharmacologic		
Losartan	Anti-fibrotic effect; cave: arterial hypotension, left ventricular outflow tract obstruction	(68,179-184). Ongoing trials: NCT01912534 (VANISH), NCT01447654 (INHERIT), NCT01150461
Diltiazem	Improves diastolic dysfunction; cave: atrioventricular block, left ventricular outflow tract obstruction	(185-187). Ongoing trials: NCT00319982
Spironolactone	Anti-fibrotic effect; cave: electrolyte disturbances, hyperkalemia, renal dysfunction	(188,189). Ongoing trials: NCT02948998, NCT00879060

Shown are evidence-based therapeutic options in hypertrophic cardiomyopathy (HCM) based on current European and North-American guidelines. Emphasis needs to be made on pharmacologic treatment options preventing the progression of pathologic remodeling in HCM. Proper staging of disease process is necessary to start preventive treatment in a timely fashion before irreversible end-stage ventricular dysfunction occurs.

whether participation in competitive sports is allowed in genotype positive/phenotype negative patients, as it is according to North-American guidelines (18), or whether no competitive sports are allowed in those patients as proposed by European guidelines (32,195).

The major cause of sudden cardiac death in HCM is ventricular fibrillation and treatment with an ICD is the only preventive measure recommended in high risk patients.

According to the European (19,32) and North-American guidelines (18,19), an ICD is recommended as secondary

prevention in HCM patients who have survived a cardiac arrest caused by ventricular fibrillation or sustained ventricular tachycardia (196,197).

For primary prevention, ICD indication is based on multiple clinical factors identified as risk factors for malignant arrhythmias and sudden cardiac death by large studies (198-201). Those risk factors include massive LV hypertrophy (>30 mm or z-score >6) (122,196,202,203), syncope of unknown etiology (204), family history of sudden death <40 y/age (205-207), non-sustained ventricular

tachycardia (122,196,205,207), and abnormal blood pressure response on stress test (196). An online available risk prediction model for sudden cardiac death in HCM (<http://www.doc2do.com/hcm/webHCM.html>) was developed based on a cohort of 3,675 patients from six centers (208). This model provides an individualized 5-year risk, based on most of the aforementioned risk factors, combined with left ventricular outflow tract (LVOT) gradient (209-211), left atrial diameter, and age at evaluation (204). The calculator classifies patients as low risk (5-year risk of SCD, <4%), intermediate risk (5-year risk of SCD, 4–6%), or high risk (5-year risk of SCD, >6%). ICD implantation is a IIB or IIA recommendation in the latter groups, respectively (212). It is of note that the online-risk calculator cannot be used in patients under the age of 16, in patients with HCM secondary to diseases other than mutations in the sarcomere, in competitive athletes, or in patients with aborted sudden death or a history of sustained ventricular tachycardia. As a caveat, the online risk-stratification-model has not yet incorporated molecular testing or CMR parameters in its current version. Therefore, the calculated risk score should not replace clinical judgment but instead should complement clinical reasoning by providing objective individualized prognostic information. Results of molecular diagnostics need to be taken into consideration since patients with compound mutations (213) or patients carrying mutations in the cardiac troponin T (214-216) are at higher risk for sudden cardiac death (217). Furthermore, recent studies provide evidence that late gadolinium enhancement on CMR with contrast counts as risk factor for malignant arrhythmias (126,147).

Pharmacotherapy

For a patient with HCM but no symptoms, no drugs are recommended by current ACC and ESC guidelines (19).

In the presence of LVOT obstruction, diastolic dysfunction and heart failure, β -blockers are the most commonly used pharmacological agents and the first choice in the absence of a contraindication (*Table 4*). The proposed mechanisms of effects include improved ventricular relaxation and increased diastolic filling time and, hence, improved left ventricular end diastolic pressure as well as perfusion (175,218). The benefits of β -blockers on mortality and the risk of SCD in patients with HCM and their impact on prevention or reversal of cardiac hypertrophy in HCM remains to be established.

Disopyramide is a negative inotropic agent and may reduce symptoms further in patients with LVOTO when added to β -blockers in patients with LVOT obstruction (176) (*Table 4*). However, this medication is not available in all countries.

L-type calcium channel blockers, such as verapamil or the non-dihydropyridine calcium channel blocker diltiazem, may be beneficial in patients who do not tolerate or respond to β -blockers (219), but they are contraindicated in patients with LVOT obstruction and in children. Verapamil and diltiazem exert their beneficial effects in part through their negative inotropic and chronotropic effects and in part through improving myocardial diastolic properties (*Table 4*).

Diuretics may be used in patients with HCM, pulmonary congestion, and heart failure, but minimal effective doses and careful observation are required to avoid hypovolemia, hypotension, and intensification or provocation of LVOT obstruction (*Table 4*).

Long-term anticoagulation is necessary in patients with persistent and paroxysmal atrial fibrillation because of risk for thromboembolism (121) (*Table 4*).

The conventionally used pharmacological agents in treatment of patients with HCM have not been shown to reverse or attenuate established cardiac hypertrophy and fibrosis, although adverse remodeling is a major determinant of mortality and morbidity in patients with HCM. Thus, effective treatment of HCM needs to target the molecular mechanisms that are involved in the pathogenesis of the phenotype. Pharmacological strategies aimed at preventing development of LV hypertrophy and adverse remodeling stage have been proposed, based on encouraging preclinical data with agents such as statins, losartan, diltiazem and others (68,179,220-223) (*Table 4*). Studies in animal models of HCM suggest possible prevention of progression to adverse remodeling stage with angiotensin I receptor blockers (68,179), calcium channel blockers, statins (220,221), mineralocorticoid receptor blockers (222), and antioxidant N-acetylcysteine (223). Although some preliminary studies in humans suggested a similar effect of those therapies in humans (180), data at this point are contradictory (180,181,224) and multiple clinical trials are currently ongoing (182,225) (*Table 4*). Specific treatments targeting cardiomyocyte energy deficiency, microvascular dysfunction and the development of fibrosis are currently being investigated (190). RNA based therapies in HCM have so far been shown to be efficient in mouse models (226) and in several *in vivo* studies (227), but no clinical trials have been undertaken so far due to delivery

system and safety problems (228).

A promising new agent might be MYK-461, an orally administered small molecule that allosterically inhibits myosin ATPase activity and diminishes myocyte force production. MYK-461 has been shown to suppress development of cardiac hypertrophy, myocyte disarray, and fibrosis in a mouse model of HCM (52). After successful completion of 3 phase I clinical trials with this compound, it is now being evaluated in a phase II clinical trial in patients with HCM and LVOT obstruction (NCT02842242).

Care needs to be taken since any medication that may cause peripheral vasodilation and afterload reduction (e.g., ACE-inhibitors, angiotensin-I receptor blockers, dihydropyridine calcium channel blockers, nitrates), intravascular volume depletion (e.g., diuretics), or positive inotropy (e.g., digoxin or inotropic agents) can worsen the LV-outflow tract obstruction and should be avoided in patients with HCM and obstructive physiology.

Invasive management

The consensus document recommends that patients with drug refractory LVOT obstruction (systolic pressure gradient of equal or greater than 50 mmHg at rest or with provocation) should be considered for septal reduction therapy, either surgical septal myectomy or alcoholic septal ablation (19) (*Table 4*). Both techniques of septal reduction therapy are highly operator dependent. The final decision as to which approach should be selected in any given patient is dependent up patient preference and the availability and experience of the operator and institution at which the patient is being treated.

Left ventricular assist devices and heart transplantation are necessary in end-stage HCM patients with drug-refractory heart failure (229). Although post-transplant survival in HCM is excellent, waitlist mortality remains substantial (230,231).

Surgical septal myectomy

Surgical septal myectomy (177) is the gold-standard for the relief of drug-refractory symptoms in patients with obstructive HCM (32,178) and improves survival, exercise capacity and quality of life in those patients (232,233). When performed by experienced operators working in high-volume centers, septal myectomy by a transaortic approach is highly effective with low perioperative mortality rate (234). Midventricular or apical myectomy is rarely

performed by the transapical approach for patients with HCM variants and refractory heart failure symptoms with the purpose to increase the left ventricular end diastolic and systolic dimensions resulting in an increase in stroke volume (235). Left ventricular outflow obstruction is often aggravated by an abnormal mitral valve and subvalvular apparatus (236). In most patients mitral regurgitation related to systolic anterior motion of the mitral valve is relieved through adequate myectomy with or without papillary muscle reduction (237). If intrinsic mitral valve disease is present, mitral valve plasty should be the first-line treatment preferred over mitral valve replacement (238,239).

Alcohol septal ablation

Catheter-based alcohol septal ablation to create a septal infarction has emerged as a less invasive percutaneous alternative to surgical septal myectomy. The results of alcohol septal ablation are dependent on the septal perforator artery supplying the area of the contact between the hypertrophied septum and the anterior leaflet of the mitral valve. A transradial approach has been shown to be associated with fewer access-related complications compared to the classical femoral artery access (240,241). There is a substantial risk for developing complete atrioventricular block requiring pacemaker implantation after performing alcohol septal ablation (242) and the literature tends to support better long-term symptom relief in those patients who undergo surgical septal myectomy (243,244). At this point, young patients and patients requiring repair of associated abnormalities of the mitral valve and/or anomalous papillary muscles are not good candidates for alcohol septal ablation (245).

Biomarkers

Since preventative treatment is necessary to avoid disease progression in HCM patients, clinical disease stages need to be diagnosed in a timely fashion. The clinical utilities of plasma biomarkers in evaluation of cardiac hypertrophy and myocardial fibrosis in HCM remain to be established. However, there is evidence for cleavage products of collagen synthesis and degradation, as well as elevated levels of cytokines, cardiac troponin T, and other markers of myocardial inflammation as biomarkers for interstitial fibrosis (88,246-248). Circulating levels of several microRNAs (especially miR29a) are elevated in HCM (72,249) and may serve as markers for cardiac hypertrophy and interstitial fibrosis (250,251).

Summary

HCM is a highly prevalent disease and genetic discoveries have contributed to our understanding of the molecular disease pathogenesis.

Molecular diagnostics and new imaging modalities have optimized patient management. Mortality in HCM has significantly decreased by applying current standard therapeutic measures, such as the prevention of sudden death by prohibition of competitive sport participation and the implantation of cardioverter-defibrillators if indicated, as well as symptomatic heart failure therapies or cardiac transplantation.

However, therapies at this point are solely supportive and there is a lack of preventive or curative therapeutics.

In the future it is anticipated that the field will shift from targeting phenotypes, such as myocyte hypertrophy, fibrosis, arrhythmias, and LVOT obstruction, toward altering the underlying molecular pathways to prevent adverse remodeling disease stage. The timing of initiation of those preventive therapies is crucial because greatest potential occurs before conversion to end-stage disease. Modern imaging technologies and identification of new biomarkers will help in identifying progression of disease stages.

It is hoped that insights from clinical studies and basic science research will allow a shift from general approaches to tailored management according to individual needs in patients with HCM.

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Footnote

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