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Chapter

Hypertrophic Cardiomyopathy: Genetics, Pathogenesis, Diagnosis, Clinical Course and Therapy

Davide Lazzeroni and Claudio Stefano Centorbi

Abstract

Hypertrophic cardiomyopathy (HCM) is a genetic disorder of cardiac myocytes that is characterized by cardiac hypertrophy, unexplained by the loading conditions, a non-dilated left ventricle and a normal or increased left ventricular ejection fraction (LV-EF). Prevalence of HCM has been estimated at 0.16% to 0.29% (≈ 1:625–1:344 individuals) in the general adult population. HCM represents the most common genetic heart disease and represent an archetypical single gene disorder with an autosomal dominant pattern of inheritance and historically termed a "disease of the sarcomere". The precise mechanisms by which sarcomere variants result in the clinical phenotype have not been fully understood. Mutant sarcomere genes trigger several myocardial changes, leading to hypertrophy and fibrosis, which ultimately result in a small, stiff ventricle with impaired systolic and diastolic performance despite a preserved LV-EF. The most common differential diagnosis challenges in the presence of hypertrophic heart disease are represented by: athlete's heart, hypertensive heart and other cardiomyopathies mimicking HCM. A multimodality approach using ECG, echocardiography, CMR, cardiac computed tomography (CCT) and cardiac nuclear imaging provides unique information about diagnosis, staging and clinical profiles, anatomical and functional assessment, metabolic evaluation, monitoring of treatment, follow-up, prognosis and risk stratification, as well as preclinical screening and differential diagnosis. HCM may be associated with a normal life expectancy and a very stable clinical course. However, about a third of patients develop heart failure (HF); in addition, 5–15% of cases show progression to either the restrictive or the dilated hypokinetic evolution of HCM, both of which may require evaluation for cardiac transplantation. The clinical course of HCM has been classified into four clinical stages: non-hypertrophic, classic, adverse remodeling and overt dysfunction phenotype. No evidence-based treatments are available for non-hypertrophic HCM patients (pre-hypertrophic stage), on the other hand in classic HCM, adverse remodeling and overt dysfunction phenotype, pharmacological or interventional strategies have the target to improve functional capacity, reduce symptoms, prevent disease progression. Therapeutic approach mainly differs on the basis of the presence or absence of significant obstructive HCM. Adult patients with HCM report an annual incidence for cardiovascular death of 1–2%, with sudden cardiac death (SCD), HF and thromboembolism being the main causes of death; the most commonly recorded fatal arrhythmic event is spontaneous ventricular fibrillation. For this reason, SCD risk estimation is an integral part of clinical management of HCM. International guidelines suggest the evaluation of several risk factor for SCD based on personal and family history, non-invasive testing including echocardiography, ambulatory

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electrocardiographic 24 hours monitoring and CMR imaging in order to identity those patients most likely to benefit implantable cardioverter-defibrillator (ICD) implantation. The present chapter summarize genetics, pathogenesis, diagnosis, clinical course and therapy of HCM as well as novel therapeutic options.

Keywords: hypertrophic cardiomyopathy, left ventricular hypertrophy, genetics, sudden cardiac death, heart failure, echocardiography, cardiac magnetic resonance, athlete's heart, hypertrophic phenocopies

1. Introduction

1.1 Definition and epidemiology

Cardiomyopathies are defined by structural and functional abnormalities of the ventricular myocardium that are unexplained by flow-limiting coronary artery disease or abnormal loading conditions [1]. Historically, cardiomyopathies has been subdivided into primary disease, in which the heart is the only involved organ, and secondary forms where the cardiomyopathy is a manifestation of a systemic disorder. Hypertrophic cardiomyopathy (HCM) is a genetic disorder of cardiac myocytes that is characterized by cardiac hypertrophy, unexplained by the loading conditions, a non-dilated left ventricle (LV) and a normal or increased left ventricular ejection fraction (LV-EF) [2]. HCM is a disorder without a distinct geographic, ethnic or gender pattern of distribution. Prevalence of HCM has been estimated at 0.16% to 0.29% (≈ 1:625–1:344 individuals) in the general adult population [2–5]. HCM is characterized by highly variable genotype–phenotype relationship with intra- and inter-family expressivity and incomplete penetrance. Given the age-dependent expression of HCM mutations, its prevalence is expected to be higher in older subjects; in fact, HCM has been reported in 0.29% (1:333) of 60-year-old individuals undergoing echocardiography for cardiovascular evaluation. [2–5]. Moreover, a much higher estimate of 0.6% (1:167) has been suggested using more sensitive imaging methods, when family members are evaluated and when genetic testing is more widely used [6–8]. On the other hand, in children cardiac hypertrophy could result from the phenocopy conditions, which might account for 5% to 10% of the clinically diagnosed HCM cases [9–11].

2. Genetics

HCM represents the most common genetic heart disease reported in populations globally. HCM is an archetypical single gene disorder with an autosomal dominant pattern of inheritance, whereby a single mutation is usually sufficient to cause the disease, albeit with variable penetrance and expression [12]. Autosomal recessive and X-linked modes of inheritance have been described but are rare [13, 14]. Approximately 60% of patients with HCM have a clearly recognizable familial disease. On the other hand, despite the great advances of the research in the field of genetics in cardiomyopathies, to date about 40% of HCM shows negative genetic testing or variants of non-certain significance. These data suggest that even non-genetic factors could contribute to the development of HCM. Moreover, a substantial proportion of patients with HCM are currently without any evidence of a genetic etiology to their disease, including a subgroup who also have no other affected family members (named "non-familial" HCM) [15]. For these reasons, the absence of an identified causative mutation should not allow to exclude a diagnosis in the presence of diagnostic criteria for HCM. Historically, HCM was termed a

"disease of the sarcomere" when the first three disease genes encoding components of the contractile apparatus of heart muscle were identified [16]. However, a wide variety of non-sarcomeric genes has been associated with HCM, thus suggesting that LV hypertrophy in HCM may not be a consequence of exclusive sarcomeric mutations. Among the known causal genes (**Figure 1**), thick myofilaments proteins such as MYH7 and MYBPC3 (myosin- binding protein C) are the 2 most common, together being responsible for approximately half of the patients with familial HCM [17–20]. On the other hand, mutations in thin myofilament proteins such as TNNT2, TNNI3 (cardiac troponin I) and TPM1 (α-tropomyosin) are relatively uncommon causes of HCM and together are responsible for less than 10% of cases [19–22]. Mutations in ACTC1 (cardiac α-actin), MYL2 (myosin light chain 2), MYL3 (myosin light chain 3), and CSRP3 (cysteine and glycine-rich protein 3) are also established, albeit uncommon, causes of HCM [23–25]. Moreover, mutations in TTN (titin), TCAP (telethonin), MYOZ2 (myozenin 2), TRIM63 (ubiquitin E3 ligase tripartite motif protein 63 or MuRF1), and FHL1 (four-and-a-half LIM domains 1) also have been implicated as causes of HCM but occur typically in sporadic cases and small families [26–33]. On the other hand, mutations in TNNC1 (cardiac troponin C), MYH6 (myosin heavy chain or α-myosin heavy chain), PLN (phospholamban), CAV3 (caveolin3), ALPK3 (α kinase 3), and JPH2 (junctophilin-2) have also been reported in patients with HCM [34–39] but their causal role in HCM is less certain and has not been established unambiguously. An X-linked inheritance typically raises the possibility of a phenocopy condition, such as Fabry disease [40]. A phenocopy condition also occurs in syndromic diseases, such as the Noonan syndrome and in storage diseases, such as Anderson–Fabry disease. [41, 42]. Finally, a subset of HCM patients (≈5%) exhibits 2 (digenic) or more (oligogenic) causal mutations in the same gene or causal mutations in different genes [20, 43–51] and the severity of LV hypertrophy in subjects with

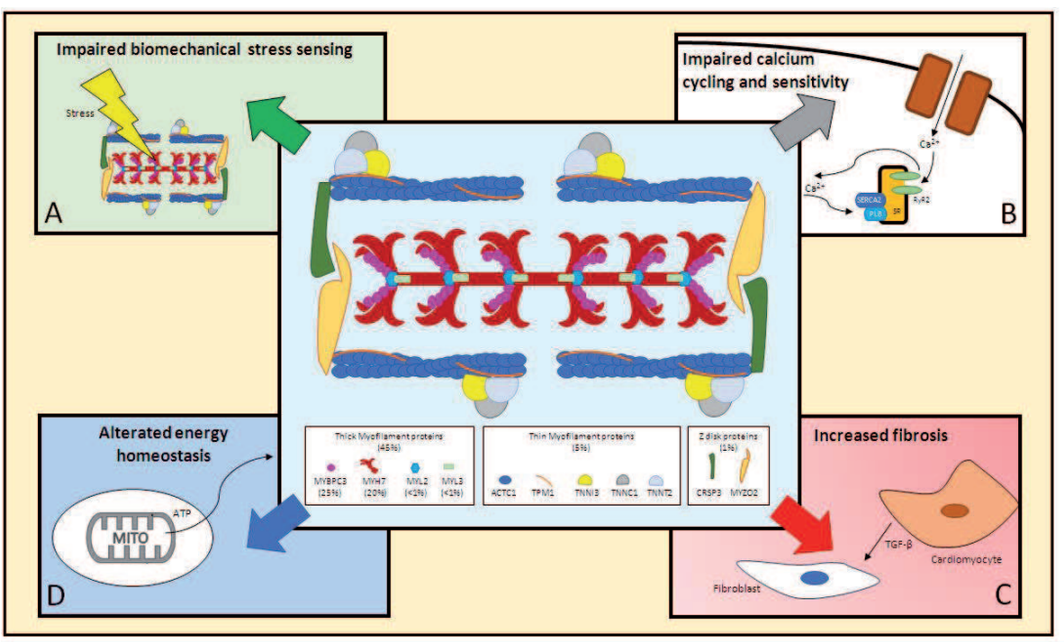

Figure 1.
HCM genetics and pathogenetic mechanisms. Center part: A schematic structure of a sarcomere composed of thick and thin filaments and Z discs is showed along with its protein constituents. Established causal genes for HCM and their relative population frequencies are listed. Panel A-D: HCM pathogenetic pathways (not be considered in isolation since they can act in concert). Panel a: Biomechanical stress sensing pathway. Panel B: Calcium cycling and sensitivity pathway. Panel C: Energy homeostasis pathway. Panel D: Fibrotic pathway. Abbreviations: LTCC, voltage-dependent L-type calcium channel; PLB, cardiac phospholamban; RyR2, ryanodine receptor 2; SERCA2, sarcoplasmic/endoplasmic reticulum calcium ATPase 2; SR, sarcoplasmic reticulum; TGF-β, transforming growth factor β; MITO, mitochondria.

such mutations seems to be more pronounced [44–48]. The majority of the causal mutations in HCM are missense mutations which may alter protein structure and function by changing the amino acid composition of the encoding protein. The insertion/deletion mutations induce a frameshift in the encoded protein. Likewise, the premature truncated proteins are subsequently degraded by the ubiquitin proteasome system, leading to haplo-insufficiency [19, 20, 52]. The missing causal gene in HCM might be in part because of the difficulty in ascertaining the causality of the genetic variants, in an unambiguous manner, in the sporadic cases and small families [53]. In general, genetic variants exert highly variable biological consequences, ranging from large and causal to clinically negligible [54–56]. The demonstration of an association between a candidate gene and the HCM phenotype in a discovery population is considered provisional (ie, hypothesis-generating) and requires testing for replication in an independent population.

3. Pathogenesis

The precise mechanisms by which sarcomere variants result in the clinical phenotype have not been fully understood. Mutant sarcomere genes trigger several myocardial changes, leading to hypertrophy and fibrosis, which ultimately result in a small, stiff ventricle with impaired systolic and diastolic performance despite a preserved LV-EF [57]. On the other hand, abnormal sarcomeric proteins may not be solely responsible for all of the clinical characteristics observed in patients with HCM. Diverse disease features including abnormal intramural coronary arteries, responsible for small vessel ischemia, elongated mitral valve leaflets, as well as congenital anomalies of the sub-mitral valve apparatus, appear to have no known direct association with sarcomere mutations. From a metabolic viewpoint, mutations in sarcomeric proteins generally increase myofilament activation and result in myocyte hypercontractility and excessive energy use [58] due to higher (disproportionate) mitochondrial activity (**Figure 1**). Mitochondrial impairments in the cardiac energy-sensing apparatus (e.g., AMP-activated protein kinase [AMPK]) as well as alterations in calcium handling result in a stimulation of signaling pathways (e.g., the Janus-associated kinase–signal transducers and activators of transcription [JAK–STAT] signaling pathway) that contribute to myocyte relaxation abnormalities and growth, with aberrant tissue architecture abnormalities such as myofibrillar disarray and myocardial fibrosis [59–62].

4. Diagnosis

4.1 Diagnostic criteria

In 2014 ESC Guidelines, HCM is defined by a wall thickness ≥ 15 mm in one or more LV myocardial segments - as measured by any imaging technique (echocardiography, cardiac magnetic resonance imaging (CMR) or computed tomography (CT) - that is not explained solely by loading conditions, thereby including both sarcomeric and non-sarcomeric mutations, such as other genetic disorders (inherited metabolic and neuromuscular diseases, chromosome abnormalities) genetic syndromes and non-genetic disorders (e.g. senile-TTR and AL amyloidosis) [2]. On the other hand, in 2020 AHA Guidelines, HCM is defined as a disease state in which morphologic expression is confined solely to the heart and characterized predominantly by LVH (wall thickness ≥ 15 mm) in the absence of another cardiac, systemic, or metabolic disease capable of producing the magnitude of hypertrophy

evident in a given patient and for which a disease-causing sarcomere (or sarcomere-related) variant is identified, or genetic etiology remains unresolved [57].

Genetic and non-genetic disorders can present with lesser degrees of wall thickening (13–14 mm). In these cases, the diagnosis of HCM requires evaluation of other features including family history, non-cardiac symptoms and signs, electrocardiogram (ECG) abnormalities, laboratory tests and multi-modality cardiac imaging [2]. More limited LVH can be diagnostic in family members of HCM patients or with a positive genetic test [57]. Children, as in adults, the diagnosis of HCM requires an LV wall thickness more than two standard deviations greater than the predicted mean (z-score: defined as the number of standard deviations from the population mean) [63]. In first-degree relatives of HCM patients with unequivocal disease (LVH ≥15 mm) the diagnosis is based on the presence of otherwise unexplained increased LV wall thickness ≥ 13 mm in one or more LV myocardial segments, as measured using any cardiac imaging technique [echocardiography, cardiac magnetic resonance (CMR) or CT].

4.2 Differential diagnosis: *"from athlete's heart to HCM phenocopies"*

The most common differential diagnosis challenges in the presence of hypertrophic heart disease are represented by: athlete's heart, hypertensive heart and other cardiomyopathies mimicking HCM.

4.2.1 Athlete's heart

HCM is the most common cause of sudden cardiac death (SCD) among athletes [64]. Systematic and endurance training can lead to physiologic LV hypertrophy thereby mimicking mild forms of HCM [64]. Distinguishing between these two forms represents an important diagnostic dilemma during athlete cardiac evaluation, thus a combination of anamnestical, clinical and instrumental data is crucial to distinguish the physiological hypertrophy seen in athlete's heart from the pathological one seen in HCM. A positive family history of SCD represent an important factor that may point towards a genetic cardiomyopathy; similarly, ECG abnormalities such as ST depression, T wave inversion, abnormal Q waves or QRS axis increase the likelihood of HCM. On the other hand, isolated positive ECG criteria for hypertrophy are not enough to suspect HCM in the athlete [64]. Even in the presence of septal thickness values suspected for mild form of HCM (ranging form 14–16 mm), in the athlete's heart echocardiogram generally presents several characteristics that are uncommon in HCM such as: normal or dilated LV volumes or normal systolic and diastolic function evaluated both with traditional methods (M-Mode or 2D) and with tissue Doppler or strain echocardiography. Moreover, a reduction in LV wall thickness after a period of deconditioning points to physiological hypertrophy [65]. In some cases, further investigations such as exercise testing (arrhythmias or abnormal blood pressure response), 24 hours ECG monitoring (arrhythmias), CMR (fibrosis) or genetic testing (causative mutations) are needed to define the presence of HCM. **Table 1** summarizes the clinical-instrumental aspects most useful in the differential diagnosis between HCM and athlete's heart.

4.2.2 Hypertensive heart

Left ventricular hypertrophy secondary to arterial hypertension can be difficult to distinguish from mild forms of non-obstructive HCM caused by sarcomeric mutations; moreover an overlap between primary and secondary LV hypertrophy could be present in up to 25% of adult HCM patients with arterial hypertension [66].

	Inheritance	**Signs or symptoms** ***of multi-organ involvement***	**ECG abnormalities** ***beyond LVH criteria***	***Routine*** **laboratory tests**	**Echocardiography**	**CMR** ***(LGE)***
Athlete's heart.	None	Uncommon	Isolated LVH	Not specific	LVH symmetrical or eccentric (mild-to-moderate). Normal systolic and diastolic function	Negative
Hypertensive heart	None	Uncommon	ST and T abnormalities	Not specific	LVH: usually concentric (mild-to-moderate)	Mild degree No specific pattern
HCM	AD	Uncommon	High LVH ST and T abnormalities Giant T wave inversion. Q waves.	Not specific	Moderate-to-severe LVH (asymmetrical and septal but potentially found at any location). Diastolic dysfunction, the LVOT obstruction Mitral valve abnormalities (mitral SAM, leaflets elongation, dysplasia, prolapse, chordal elongation, laxity and hypermobility). Atrial enlargement. Apical aneurysm	Frequent RV insertion points and Intramural potentially found at any location
Anderson–Fabry disease	X-linked	Visual impairment Sensorineural deafness Paraesthesiae/ sensory abnormalities Angiokeratoma	Short P-R / preexcitation AV block	Proteinuria with/without glomerular filtration rate	Concentric LVH Increased atrioventricular valve thickness Increased RV free wall thickness Global hypokinesia (with/without LV dilatation)	Frequent Posterolateral LGE in concentric LVH
Familiar amyloidosis	AD	Visual impairment Paraesthesiae/ sensory abnormalities Carpal tunnel syndrome (bilateral)	Low QRS voltage AV block	Proteinuria with/without glomerular filtration rate	Increased interatrial septum thickness and atrioventricular valve thickness. Increased RV free wall thickness. Pericardial effusion. Ground-glass appearance of myocardium. Global hypokinesia (with/without LV dilatation)	Frequent Diffuse subendocardial LGE "zebra" pattern Intense myocardial 'avidity' for Gadolinium

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	Inheritance	Signs or symptoms *of multi-organ involvement*	ECG abnormalities *beyond LVH criteria*	*Routine* laboratory tests	Echocardiography	CMR *(LGE)*
Danon disease	X-linked	Learning difficulties, mental retardation Visual impairment	Short P-R / preexcitation AV block Extreme LVH (Sokolow >100)	↑Creatine kinase ↑ Transaminase	Extreme concentric LVH. Global hypokinesia (with/without LV dilatation)	Frequent Large amount subendocardial or transmural
Mitochondrial cardiomyopathy	X-linked or matrilinear	Sensorineural deafness Learning difficulties, mental retardation Visual impairment Muscle weakness	Short P-R / preexcitation	↑ Creatine kinase Transaminase Lactic acidosis	Global hypokinesia (with/without LV dilatation)	Frequent Large amount Non-ischemic LGE Intramural pattern mostly confined to the basal LV inferolateral wall

Table 1.
HCM diagnosiss and differential diagnosis: "from athlete's heart to HCM phenocopies". Inheritance, signs or symptoms of multi-organ involvement, ECG abnormalities beyond LVH criteria, routine laboratory tests, echocardiographic and CMR main findings are shown for HCM and each phenocopies.

Detailed arterial hypertension history and arterial blood pressure assessment as well as clinical evaluation of relatives may be crucial in distinguishing between hypertensive heart and HCM. Moreover, a multimodality imaging approach is crucial in the differential diagnosis of HCM in hypertensive patients. Echocardiographic tissue doppler shows more impairment of diastolic function as well as lower early diastolic velocities in HCM [67, 68]. Similarly, two-dimensional (2D) strain echocardiography in HCM reveals a mid and apical short axis segments reduced radial strain as well as a reduced longitudinal strain in HCM with sarcomeric mutations [67, 68]. Moreover, myocardial fibrosis in CMR imaging as well as natriuretic peptides and troponin levels tend to be higher in HCM than in hypertensive heart [69].

4.2.3 HCM phenocopies

Significant advances and widespread availability of genetic testing at the same time have improved detection of the sarcomeric mutations that cause HCM but have also highlighted the significance of inborn errors of metabolism or metabolic storage disorders that can mimic HCM, named "HCM phenocopies" [70]. Five to ten percent of adult cases of HCM are caused by other genetic disorders including inherited metabolic and neuromuscular diseases, chromosome abnormalities, genetic syndromes as well as non-genetic disorders (e.g. TTR or AL amyloidosis) [71–74]. Whilst HCM phenocopies are relatively rare, it is crucial to distinguish these conditions at an early stage as their natural history, management, therapy and prognosis vary significantly from that of HCM with sarcomeric mutations. **Table 1** illustrates the salient features (red flags) of HCM phenocopies.

4.3 Multimodality imaging in HCM

Imaging techniques play an essential role in the evaluation of patients with HCM. A multimodality approach using ECG, echocardiography, CMR, cardiac computed tomography (CCT) and cardiac nuclear imaging provides unique information about diagnosis, staging and clinical profiles, anatomical and functional assessment, metabolic evaluation, monitoring of treatment, follow-up, prognosis and risk stratification, as well as preclinical screening and differential diagnosis (**Figure 2**).

ECG: is recommended at the first clinic visit in all individuals with known or suspected HCM and should be repeated whenever there is a change in symptoms in patients with an established diagnosis. It can be normal at presentation but generally shows a variable combination of LV hypertrohy (LVH), ST- and T-wave abnormalities and pathological Q-wave; ECG abnormalities that could mimicks other conditions, such as myocardial ischaemia or infarction, when interpreted together with echocardiography and CMR imaging findings, can suggest an underlying diagnosis or provide clues to the distribution of LVH and myocardial scar [75]. Moreover, since ECG abnormalities generally precede the development of LVH, periodic clinical and instrumental evaluations as well as family screening are useful even in the absence of conclusive diagnostic criteria. The frequency of arrhythmias detected during ambulatory electrocardiographic monitoring is age-related; asymptomatic non-sustained ventricular tachycardia (NSVT) occurs in 25% of adults with HCM and for this reason a 24 or 48 hour Holter ECG represents a primary test for estimate the risk of SCD [2, 76–77].

Echocardiography: is the central imaging technique to the diagnosis and monitoring of HCM, given that identifies and quantify LVH that generally is asymmetric and involving the interventricular septum in the basal LV segments but often extends into the lateral wall, the posterior septum and LV apex [78]. In fact, increased ventricular wall thickness can be potentially found at any location.

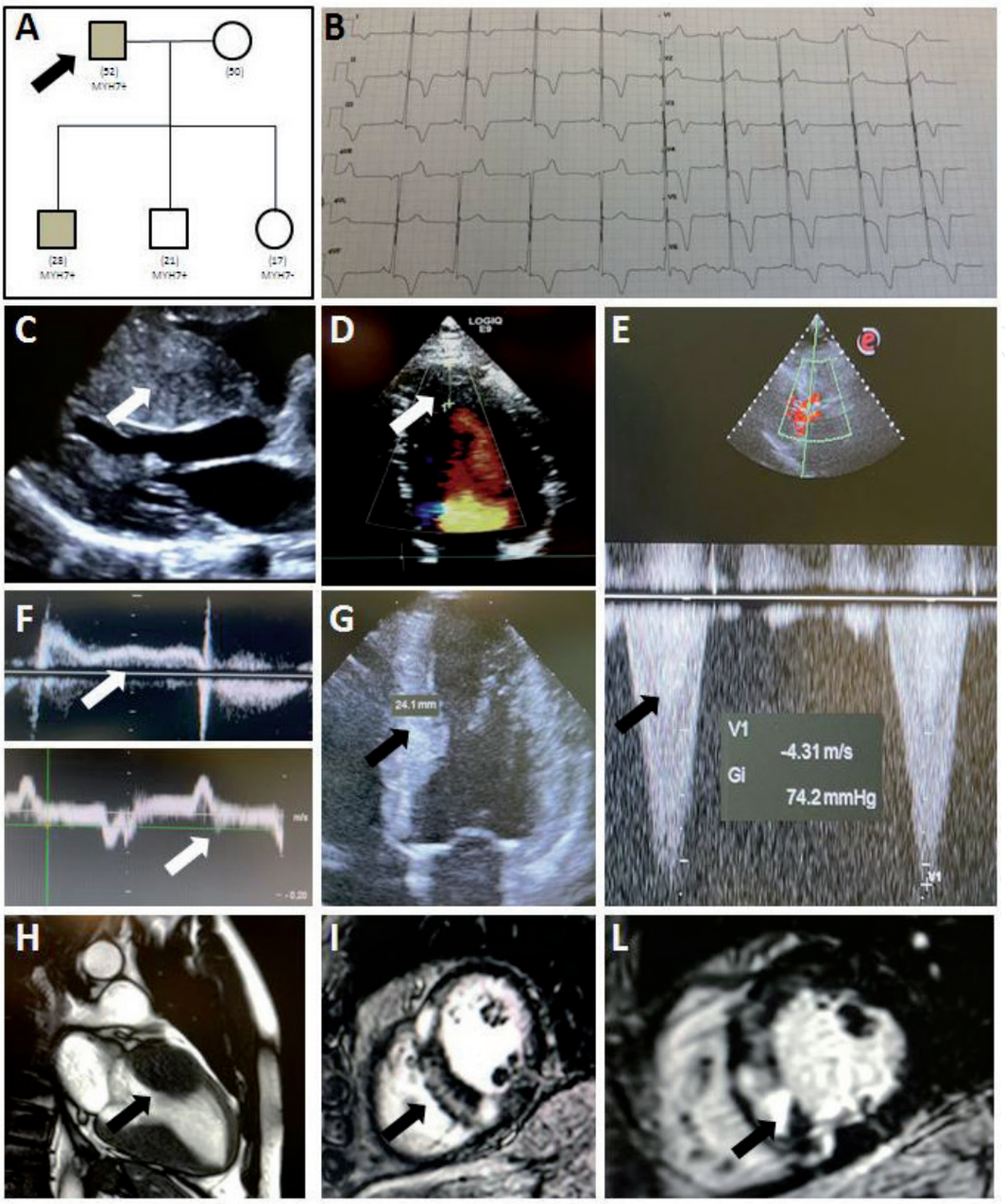

Figure 2.
*HCM: Inheritance and multimodality imaging. Panel A shows an HCM family pedigree with a MYH7+ mutation (autosomal dominant inheritance). The father and two of his children had HCM, another child was unaffected and was excluded from further clinical testing, and one child had a pathogenic mutation without LV hypertrophy. Black symbols denote affected family members, white symbols unaffected family members, squares male family members, and circles female family members; the arrow indicates the proband. The numbers under the symbols indicate age (in years) at the time of testing. Panel B shows ECG abnormalities in HCM characterized by: Short PR-interval, high QRS voltage, ST depression followed by diffuse giant T wave inversion. Panel C: HCM with extreme asymmetrical septal hypertrophy (45 mm – Echocardiography). Panel D: Apical HCM (echocardiography). Panel E shows HOCM with significant left ventricular outflow-tract obstruction (74 mmHg peak gradient at echocardiography). Panel F shows a triphasic doppler inflow velocities with restrictive pattern in addition to L wave (arrow) in HCM patients with thin myofilament associated mutation (upper side). Tissue Doppler showing severe diastolic dysfunction characterized by low e' (arrow) velocities (lower side). Panel G: Severe (24 mm) septal asymmetrical hypertrophy (arrow) in HCM (echocardiography). Panel H: Severe septal asymmetrical hypertrophy (arrow) in HCM (cardiac magnetic resonance). Panel I: HCM with fibrosis (cardiac magnetic resonance – LGE - arrow) at RV insertion points and intramural in the intraventricular septum. Panel L: HCM with diffuse and marked intramyocardial fibrosis (cardiac magnetic resonance – LGE - arrow) (**Figure 3**).*

Moreover, echocardiography estimates systolic and diastolic function, the presence of left ventricular outflow tract (LVOT) obstruction at rest and/or under provocative maneuvers such as Valsalva or standing, midventricular obstruction, mitral

valve abnormalities (mitral SAM, leaflets elongation with excessive tissue, dysplasia and prolapse, chordal elongation, laxity and hypermobility), atrial enlargement, or apical aneurysm [79]. Stress echocardiography can be used to detect myocardial ischemia, significant misunderstood LVOT obstruction, symptoms and blood pressure response to exercise [80].

Cardiovascular magnetic resonance (CMR) imaging: provides detailed information on cardiac morphology, ventricular function and myocardial tissue characteristics [81]. CMR estimate left ventricle volumes, mass, ejection fraction as well as quantification, location, type and distribution of LVH but especially the visualization and quantification of myocardial fibrosis (LGE) [80].

In detection of myocardial ischaemia CCT is useful to evaluate the presence of epicardial coronary artery disease (CAD) in patients with HCM.

Single photon emission computed tomography/position emition tomography (SPECT/PET) myocardial perfusion imaging (using Thallium-201 and Tc-99 m labeled tracers) is useful to evaluate the presence of coronary microvascular dysfuntion showing reversible and fixed defects, thereby suggesting ischaemia and scar, with or without epicardial CAD detecting [82]. The assessment of myocardial metabolism can be performed through PET with F-18-fluorodeoxyglucose (FDG) or C-11-acetate, since an impairment in oxidative and glucose metabolism, mainly in the hypertrophic myocardium, has been found in HCM [83]. PET imaging has also been used to assess cardiac autonomic dysfunction, given that increased local catecholamine levels due to impaired neurotransmitter re-uptake into the cardiac nerve terminals, leading to decreased myocardial beta-adrenoceptor density, has been found in HCM [84].

Cardiopulmonary exercise testing (CPET): provides objective information about the severity of functional limitation, mechanisms responsible for symptoms during effort and plays a central role for cardiac transplantation indication [85]. CPET may be helpful in differentiating HCM from physiological ventricular hypertrophy since maximal oxygen consumption is normal or supra-normal in athlete's heart and reduced in HCM. Moreover, CPET or conventional treadmill- or bicycle ergometry may be used in several contests: initial clinical evaluation, change in symptoms, LVOT gradient evaluation during effort, blood pressure response during exercise, detecting signs of myocardial ischemia caused by epicardial CAD and/or microvascular dysfunction [86–90].

5. Clinical course and disease stanging

HCM may be associated with a normal life expectancy and a very stable clinical course. However, about a third of patients develop heart failure (HF); in addition, 5–15% of cases show progression to either the restrictive or the dilated hypokinetic evolution of HCM, both of which may require evaluation for cardiac transplantation [91, 92]. The clinical course of HCM has been masterfully classified by Olivotto et al. into four clinical stages: non-hypertrophic, classic, adverse remodeling and overt dysfunction phenotype [93] (**Figure 3**).

Non-hypertrophic HCM: is characterized by the absence of LVH in individuals with HCM-causing mutations identification during systematic family screenings. This stage of the disease is more frequent in newborn or very young children, while LVH tends to manifest during the second decade of life. However, due to incomplete penetrance and age-related onset, genotype-positive individuals can develop LVH as late as the 6th or 7th decade, and a significant minority seem to never develop the disease at all [94–96]. ECG, in this contest, is a fundamental tool to identify these patients since abnormalities can usually be evident even in the absence of LVH

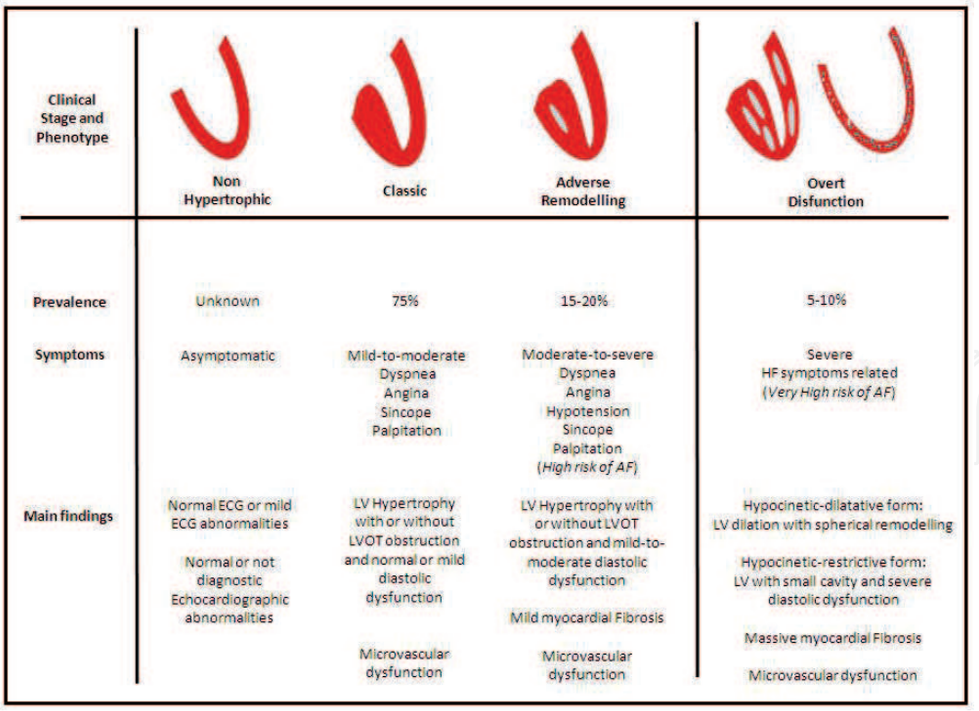

Figure 3.
Clinical stage and phenotypes of HCM: Prevalence, symptoms and main findings are separately shown for each stage of the disease.

on the echocardiogram [94]. Echocardiographic abnormalities may be found and includes impaired LV relaxation, mitral valve or subvalvar abnormalities, and mild degrees of left atrial enlargement. Although not diagnostic, these abnormalities may useful to suspect HCM in the context of familiar screening or ECG abnormalities context [79–94]. CMR shows some degree of LV hypertrophy in about 16% of genotype-positive subjects with negative echocardiography. Prognosis of genotype-positive individuals in this stage is unresolved, but presumed favorable [95, 96].

Classic HCM Phenotype: is defined as the phase in which the hypertrophic phenotype is fully expressed and the LV is hyperdynamic (as defined by an LV-EF >65%), without extensive fibrotic changes. LVH is typically regional and asymmetrical, generally involving the basal septum and anterior wall, but can potentially involve any part of myocardial muscle such as right ventricle or papillary muscles [94–97]. Moreover, a large number of mitral valve, sub-valvar, subaortic, midventricular abnormalities, atrial remodeling, coronary myocardial bridging, coronary microvascular dysfunction, crypts and autonomic nervous system abnormalities are present in this stage of the disease [79–99]. This stage is characterized by classic features such as myocardial disarray, microvascular remodeling, and interstitial fibrosis [95–101]. Most patients experience long periods of clinical stability without symptoms and may never undergo significant degrees of adverse remodeling or disease progression during their lifetime. Life expectancy is relatively favorable, with an annual cardiovascular mortality around 1% [94–102].

Adverse Remodeling Phenotype: is defined as the presence of structural modifications due to increasing LV fibrosis with worsening function (LV-EF 50%–65%) associated with relatively preserved clinical and hemodynamic balance (15% to 20% of patients) [103–105]. The definition of this intermediate stage of disease progression is based on a combination of several structural and functional features including an LV-EF in the low-normal range [106], moderate to severe diastolic dysfunction [107, 108], marked atrial enlargement [109], moderate areas of LV fibrosis [94, 106–111], severe microvascular dysfunction [112], thinning of the

LV walls [103], onset of atrial fibrillation (AF) [113], spontaneous reduction or loss of LVOT obstruction [103–114], LV apical aneurysms [115] and variable patterns of intramyocardial fibrosis [116] that is inversely related to LV-EF.

Overt dysfunction HCM Phenotype: (5% of patients) is characterized by severe functional deterioration of the LV (LV-EF < 50%) secondary by extreme degrees of fibrosis and remodeling and generally associated with hemodynamic decompensation and adverse outcome [103, 105, 110, 117–119] with accelerated clinical deterioration of clinical condition. The morpho-functional manifestation of this stage can be summarized in two distinct and opposite phenotypical patterns: the hypokinetic-dilated form (LV dilation with spherical remodeling) [95, 110, 118, 119], that often may be hard to distinguish from a primary dilated cardiomyopathy, and the hypokinetic restrictive form (LV with small cavity and extreme diastolic dysfunction), mimicking a primary restrictive cardiomyopathy [94, 118–122]. In both forms, overt dysfunction represents the extreme consequence of adverse remodeling and the outcome in this stage is severe, not only due to high rates of HF-related complications and mortality but also because of a considerable incidence of SCD [95, 118–123].

6. Management

No evidence-based treatments are available for non-hypertrophic HCM patients (pre-hypertrophic stage) and avoiding competitive activity may be considered in these individuals for the risk of development of HCM or SCD although this issue remains highly controversial [95, 124]. In classic HCM, adverse remodeling and overt dysfunction phenotype, pharmacological or interventional strategies have the target to improve functional capacity, reduce symptoms, prevent disease progression. Therapeutic approach mainly differs on the basis of the presence or absence of LVOT obstruction (HOCM). Patients with HCM who are asymptomatic and have no evidence of arrhythmias or LVOT obstruction at rest or on effort generally do not require medical treatment [125]. In symptomatic HOCM patients, the aim is to improve symptoms by using drugs, surgery, alcohol ablation or pacing. In symptomatic patients without LVOT obstruction, the target of therapy is to reduce arrhythmic risk, LV filling pressures as well as improve symptoms such as dyspnea and angina. Patients with progressive LV systolic or diastolic dysfunction refractory to medical therapy may be candidates for cardiac transplantation.

6.1 HOCM

LVOT obstruction is defined as a peak instantaneous Doppler gradient of ≥30 mm Hg and the threshold for invasive treatment is usually considered to be ≥50 mm Hg. In general, all HCOM patients should avoid dehydration and excess alcohol consumption, and weight loss should be encouraged. Arterial and venous dilators, such as nitrates and phosphodiesterase type 5 inhibitors, can exacerbate LVOT obstruction and should be avoided [126]. HOCM symptomatic patients can be treated initially with non-vasodilating ß-blockers titrated to maximum tolerated dose. If ß-blockers alone are ineffective, disopyramide can be added, titrated up to a maximum tolerated dose [127, 128] because can abolish basal LV outflow pressure gradients and improve exercise tolerance and functional capacity without pro-arrhythmic effects [129–131]. Verapamil or ditiazem can be used when ß-blockers are contraindicated or ineffective [132–135]. Patients with HOCM (gradient ≥50 mm Hg,) and drug-refractory symptoms benefit from septal reduction therapy (SRT). Both septal myectomy and alcohol septal ablation (ASA) are

reasonable options when performed at experienced centres as part of a multidisciplinary team. Septal myectomy may be preferred when additional papillary muscle or mitral valve intervention can be performed, while ASA is favored for patients with elevated surgical risk [125]. Surgical myectomy has demonstrated excellent long-term efficacy and safety at selected high-volume centres with near-complete resolution of resting and inducible LVOT gradients. ASA showed similar perioperative mortality (about 1%) when compared to myectomy [136], although associated with a 10–15% rate of complete heart block, repeat procedures and increased risk of scar-related ventricular arrhythmias [137, 138]. Moreover, ASA is dependent on coronary anatomy since 15% of patients had unsuitable septal perforators [139]. In experienced centres, selective injection of alcohol into a septal perforator artery (or sometimes other branches of the left anterior descending coronary artery) to create a localized septal scar has outcomes similar to surgery in terms of gradient reduction, symptom improvement and exercise capacity [140–144]. Even in absence of randomized trials comparing surgery and ASA, several meta-analyses have shown that both procedures improve functional status with a similar procedural mortality [145–148].

6.2 Symptomatic patients without LVOT

In patients with normal LV-EF and no evidence of resting or provocable LVOT obstruction, aim of therapy is to reduce LV diastolic pressures and improve LV filling by slowing the heart rate with b-blockers, verapamil or diltiazem and cautious use of loop diuretics. Restoration of sinus rhythm or ventricular rate control is essential in patients who have permanent or frequent paroxysms of AF and digoxin is not recommended in patients with preserved EF because of the potentially adverse effects of positive inotropic stimulation [149]. ß-Blockers or calcium antagonists should be considered in patients with exertional or prolonged episodes of angina-like pain. Both classes improve diastolic function, reduce myocardial oxygen, thereby improving stress-induced sub-endocardial perfusion defects [150–154]. Patients with reduced LV-EF and HF symptoms should be treated with diuretics, ß-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB) and mineralocorticoid receptor antagonists (MRA) according to ESC guidelines for the management of chronic heart failure [155]. Moreover, CRT may be considered in individual patients with refractory symptoms, LV-EF < 35% and LBBB (QRS duration 120 ms) in accordance with current ESC Guidelines [156]. On the other hand, since LV-EF < 50%, rather than <35% as in primary or secondary dilated cardiomyopathies, is a strong discriminator of end-stage disease (associated with deteriorating HF and SCD) there is clear need for HCM disease-specific CRT and CRT-D criteria [57].

Orthotopic cardiac transplantation should be considered in patients with moderate-to-severe drug refractory symptoms (NYHA functional Class III–IV) and no LVOTO who meet standard eligibility criteria [157].

6.3 Management atrial fibrillation and anticoagulation therapy

Atrial fibrillation (AF) is the most frequent arrhythmia in HCM, affecting more than 20% of patients, and represents a marker of unfavorable prognosis, particularly when associated with LVOT obstruction and in patients younger than 50 years of age; moreover, the onset of AF worsens symptoms related to HF [158–160]. In haemodynamically stable patients, oral b-blockers or non-dihydropyridine calcium channel antagonists are recommended to slow the ventricular response to AF [161, 162]. Given the high incidence of stroke in patients with

HCM and paroxysmal, persistent or permanent AF, the current European Society of Cardiology (ESC) Guidelines of Atrial Fibrillation invite to do not use the CHA2DS2-VASc score to calculate stroke risk recommend that all patients with AF should receive treatment with OAC [163]. Similarly, the American Heart Association and American College of Cardiology (AHA/ACC) Guidelines recommended use direct-acting oral anticoagulants (NOAC) as first-line option and vitamin K antagonists as second-line option [57].

6.4 Prevention of sudden cardiac death

Adult patients with HCM report an annual incidence for cardiovascular death of 1–2%, with SCD, HF and thromboembolism being the main causes of death; the most commonly recorded fatal arrhythmic event is spontaneous ventricular fibrillation (VF), but asystole, AV block and pulseless electrical activity are described [2]. For this reason, SCD risk estimation is an integral part of clinical management of HCM [164]. Younger HCM patients are at higher risk for SCD than older patients [30, 165–171] since the 5-year cumulative proportion of SCD events is 8–10% from diagnosis in childhood HCM [172, 173]. In secondary prevention (patients which experiment cardiac arrest due to VT or VF or spontaneous sustained VT causing syncope or haemodynamic compromise), implantable cardioverter-defibrillator (ICD) implantation is indicated in all HCM patients. On the other hand, in primary prevention the best strategy to evaluated SCD risk seems to be a multiparametric approach. Recently, AHA/ACC guidelines suggest the evaluation of several risk factor for SCD based on personal and family history [165, 174–176], noninvasive testing including echocardiography [174, 177–179], ambulatory electrocardiographic 24 hours monitoring [180, 181] and CMR imaging [180–186] in order to identity those patients most likely to benefit ICD implantation [33, 168–170, 174, 187]. On the other hand, ESC guidelines [2] have proposed a risk score, named HCM Risk-SCD, that includes both clinical and instrumental data, thereby predicting annual risk of SCD and suggesting indication for ICD implantation (**Table 2**). Subcutaneous ICD (S-ICD) may be considered in HCM patients who have no indication for pacing especially in patients that have a long life expectancy. However, particular attention should be paid to ensuring optimal R-wave sensing to avoid inappropriate shocks [2].

6.5 New therapy prospective

Novel therapeutic options are being evaluated and validated with diversified targets in the context of the physiopathology of hypertrophic cardiomyopathy.

Myocardial Contractility and energetics: Hypercontractility appears to play a central role in the pathogenesis of HCM since the vast majority of known mutations affect sarcomeric proteins, and ~70% of identifiable mutations involving cardiac beta-myosin heavy chain (MYH7) and myosin-binding protein C (MYBPC) that contain the ATPase involved in actin–myosin cross bridging and muscle fiber shortening, thereby serving as the molecular motor for myocardial contraction [188–191]. It has been hypothesized that HCM mutations increase net power generation by the sarcomere resulting in LV hypercontractility and stiffening that is clinically observed. Mavacamten, a selective allosteric inhibitor of myosin ATPase capable of reducing the formation of bridges between actin and myosin at the sarcomere level and therefore of reducing contractility and improving the energy profile of the myocardium, helps ventricular hyper-contractility which has a pathophysiological role determinant in the genesis of the dynamic obstruction to the left ventricular outflow. It has been shown to improve exercise capacity, symptoms,

SCD risk factor		Definition	AHA/ ACC	ESC
Clinical and anamnestical data	**Family history of SCD**	Sudden death judged definitively or likely attributable to HCM in ≥first-degree or close relatives who are 50 years of age.	X	X
	Age	The effect of age on SCD is incremental. No data with age < 16 or > 80		X
	Unexplained syncope	≥1 Unexplained episodes involving acute transient loss of consciousness, judged by history unlikely to be of neurocardiogenic etiology, nor attributable to LVOTO, and especially when occurring within 6 months of evaluation (events beyond 5 years in the past do not appear to have relevance).	X	X
24 ECG monitoring	**NSVT**	NSVT with runs frequent (≥3), longer (≥10 beats), and faster (≥200 bpm) occurring usually over 24 to 48 hours of monitoring. For pediatric patients, a VT rate that exceeds the baseline sinus rate by >20%.	X	X
Echocardiographic data	**Massive LVH**	Wall thickness ≥ 30 mm in any segment within the chamber by echocardiography or CMR imaging; consideration for this morphologic marker is also given to borderline values of ≥28 mm in individual patients at the discretion of the treating cardiologist. For pediatric patients with HCM, an absolute or z-score threshold for wall thickness has not been established; however, a maximal wall that corresponds to a z-score ≥ 20 (and > 10 in conjunction with other risk factors)	X	X
	LV systolic dysfunction	Systolic dysfunction with EF ≤ 50% by echocardiophy or CMR imaging	X	
	LV apical aneurism	Apical aneurysm defined as a discrete thin-walled dyskinetic or akinetic segment of the most distal portion of the LV chamber; independent of size.	X	
	Left atrial diameter	Left atrial diameter as determined by M-mode or 2D echocardiography in the parasternal long axis plane at the time of evaluation		X
	LVOT	Maximum LV outflow gradient determined at rest and with Valsalva provocation (irrespective of concurrent medical treatment)		X
Ergometric data	**Exercise blood pressure response**	A failureto increase systolic pressure by at least 20 mmHg from rest to peak exercise or a fall of > 20 mmHg from peak pressure.		X

SCD risk factor		Definition	AHA/ ACC	ESC
CMR	**Extensive LGE**	Diffuse and extensive LGE, representing fibrosis, either quantified or estimated by visual inspection, comprising ≥15% of LV mass (extent of LGE conferring risk has not been established in children).	X	
Recommendations for ICD implantation in primary prevention				
AHA/ACC		**ESC (HCM Risk-SCD score)**		
ICD is reasonable (2A) with at least one of the following: • Family history of SCD • Massive LVH • Unexplained syncope • Apical aneurism • LV-EF < 50% • NSVT (in children) **ICD may be considered (2B) with at least one of the following:** • NSVT in adults • Extensive LGE		• **LOW RISK (5-year risk < 4%):** ICD generally not indicated • **INTERMEDIATE RISK (5-year risk 4–6%)**: ICD may be indicated • **HIGH RISK (5-YEAR RISK ≥ 6%):** ICDshould be indicated		

Table 2.
Sudden cardiac death risk factors: Type, definition, AHA/ACC and ESC guidelines criteria for SCD risk assessment in primary prevention (upper side). Recommendations for ICD implantation in primary prevention according to AHA/ACC and ESC guidelines, separately (lower side).

obstruction to the outflow and quality of life in patients with HOCM. Therefore, Mavacamten represents a valid new therapeutic option (but still not available) for patients with HCM and severe obstruction to the outflow tract despite maximal doses of beta-blocker, calcium channel blockers and disopyramide and before opting for a surgical approach [192].

Ion channels Regulation. HCM is associated with enhanced late sodium current (iNaL) activity due to enzyme-induced sodium-channel phosphorylation which results in increased intracellular sodium (Na+), and in turn, calcium (Ca2+) overload through ion exchange [193]. Dysregulated Ca2+ and Na + handling may contribute to altered cardiomyocyte mechanics (hyper-contractility and impaired relaxation) and predispose the myocardium to arrhythmias. Ranolazine is an inhibitor of iNaL with several potential beneficial effects in HCM, mainly related to the improvement in myocardial relaxation and both anti-ischemia and arrhythmia effects [193]. Although a open-label study (RHYME, NCT01721967) demonstrated positive effects on clinical outcomes, data from a phase II trial (RESTYLE-HCM) failed to demonstrate a significant effect on objective measures (peak VO2, serum B-type natriuretic peptide, diastolic function), while a reduction in premature ventricular complex burden [194] has been reported. For these reasons, ranolazine still remains an intriguing area of research in the field of HCM therapeutic options.

Fibrosis. *S*everal therapies have attempted to address fibrosis and disease progression in HCM, although nowadays no drug has shown convincing benefits, this target represents an interesting field of research in cardioyopathies. While losartan, valsartan and spironolactone was demonstrated to be ineffective [195–198], atorvastatin demonstrated effects on suppression of hypertrophy in pre-clinical models [199] but had no effect and poor treatment adherence in a small early feasibility study in humans [200].

Genome editing and gene silencing. Advances in genome editing technology have sparked excitement about the potential for therapeutic use in cardiovascular disease; however, there remain important hurdles prior to implementation in clinical practice [201, 202]. Current techniques including CRISPR/Cas9 cause a double-stranded DNA break at a desired genetic locus followed by intrinsic cellular repair that is virtually error-free and recently, high-fidelity gene repair in human embryos carrying HCM mutations was shown to be feasible [203]. Using sperm from a heterozygous MYBPC3 mutation carrying male patient, oocytes from healthy women were inseminated. Simultaneous injection of a mutation-specific CRISPR/Cas9 system during early metaphase resulted in editing of the mutation 100% of the time [204]. Allele-specific gene silencing is another gene-based therapeutic technology that holds promise for monogenic diseases. This typically involves the transduction of an adenovirus vector containing short-interfering ribonucleic acid segments designed to suppress expression of a specific pathogenic allele – a method more broadly defined as ribonucleic acid interference (RNAi). In pre-clinical models, RNAi was demonstrated to attenuate the phenotype of specific mutations causing catecholaminergic polymorphic ventricular tachycardia [205], HCM [206] and restrictive cardiomyopathy [207].

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