# We are IntechOpen,
# the world's leading publisher of
# Open Access books
# Built by scientists, for scientists

## 6,900
Open access books available

## 185,000
International authors and editors

## 200M
Downloads

## 154
Countries delivered to

Our authors are among the

## TOP 1%
most cited scientists

## 12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS
**BOOK CITATION INDEX**
INDEXED

**WEB OF SCIENCE**™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

## Interested in publishing with us?
## Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

# 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% ($\approx$ 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

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% ($\approx$ 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 ($\approx$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
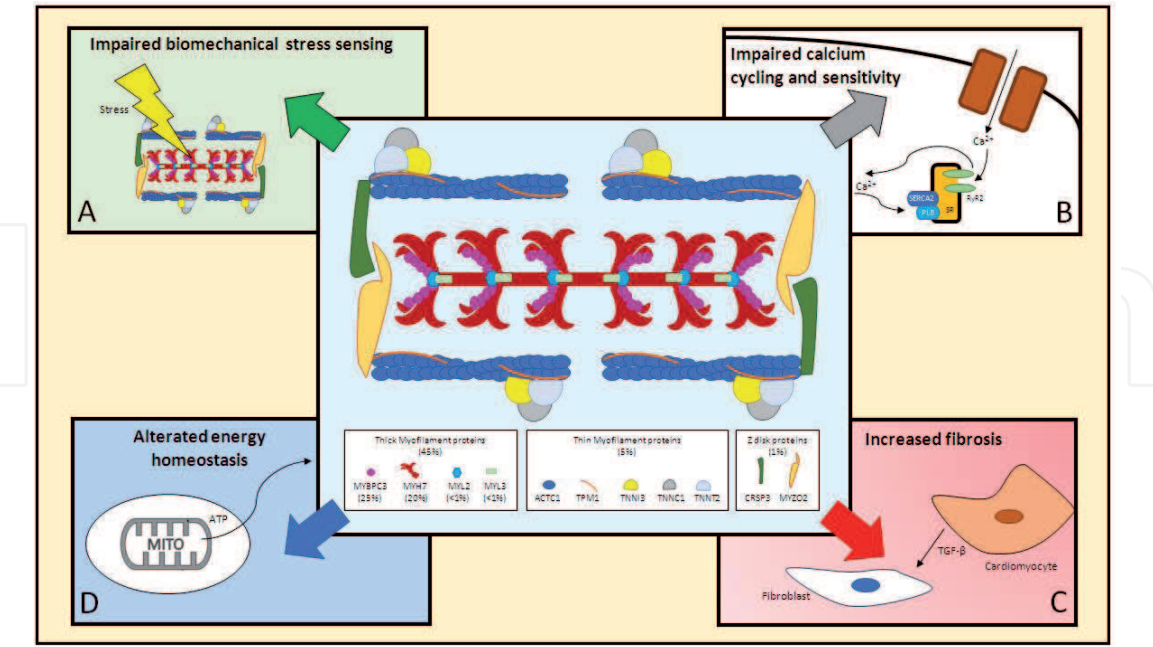


**Figure 1.**
*HCM genetics and pathogenetic mechanisms. Center part: A schematic structure of a sarcomere composed of thick and thin filaments and Z discs is showed along with its protein constituents. Established causal genes for HCM and their relative population frequencies are listed. Panel A-D: 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 |

|  | 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.
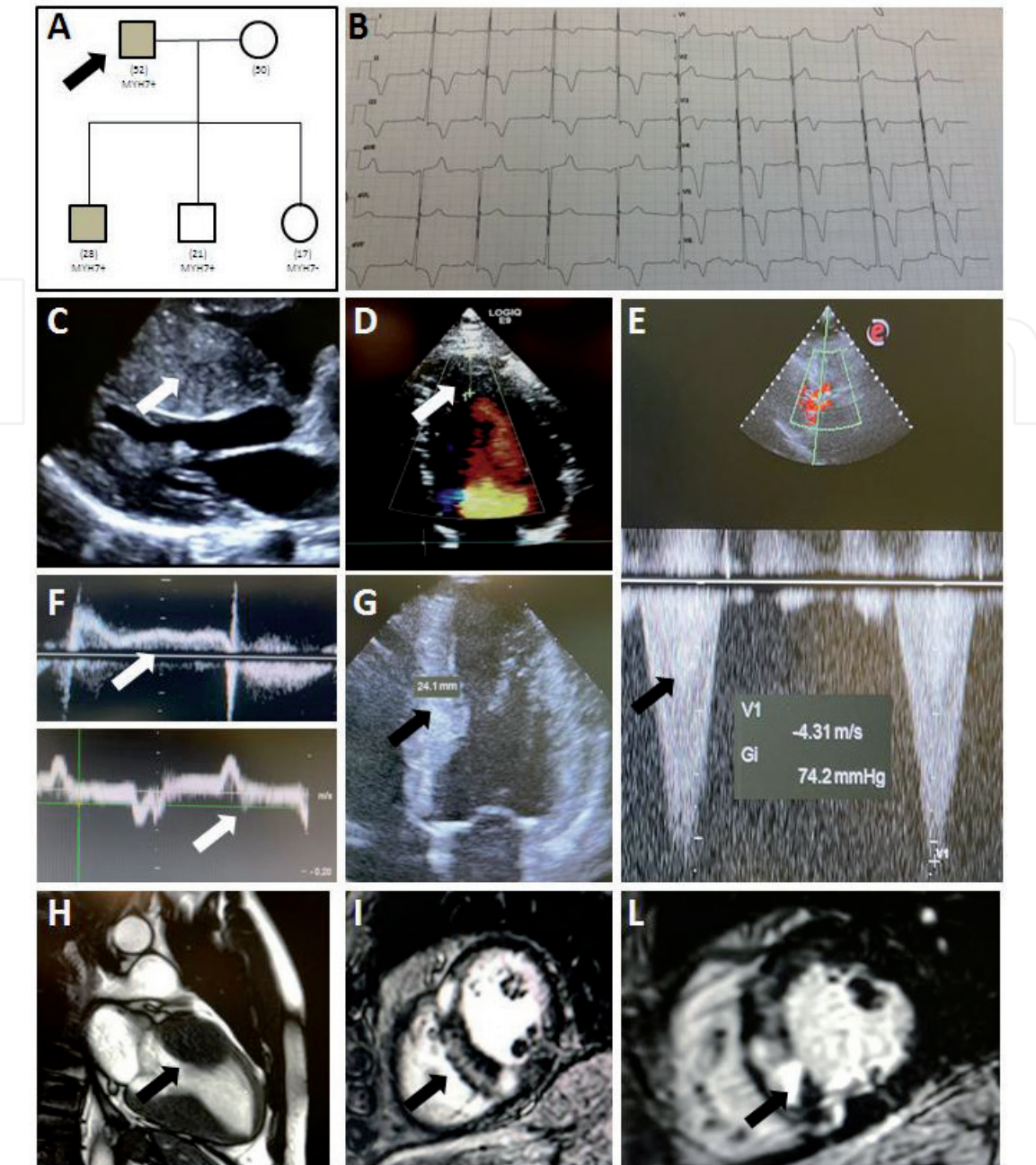
**Figure 2.**
*HCM: Inheritance and multimodality imaging. Panel A shows an HCM family pedigree with a MYH7+ mutation (autosomal dominant inheritance). The father and two of his children had HCM, another child was unaffected and was excluded from further clinical testing, and one child had a pathogenic 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 failure to 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:** <br><br> • Family history of SCD <br><br> • Massive LVH <br><br> • Unexplained syncope <br><br> • Apical aneurism <br><br> • LV-EF < 50% <br><br> • NSVT (in children) <br><br> **ICD may be considered (2B) with at least one of the following:** <br><br> • NSVT in adults <br><br> • Extensive LGE | • **LOW RISK (5-year risk < 4%):** ICD generally not indicated <br> • **INTERMEDIATE RISK (5-year risk 4–6%):** ICD may be indicated <br> • **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**. Several 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].

## Author details

Davide Lazzeroni[1]* and Claudio Stefano Centorbi[2]

1 IRCCS Fondazione Don Gnocchi, Florence, Italy

2 Fondazione Don Gnocchi, Parma, Italy

*Address all correspondence to: davide.lazzeroni@gmail.com

IntechOpen

## References

[1] Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P, Dubourg O, Kuhl U, Maisch B, McKenna WJ, Monserrat L, Pankuweit S, Rapezzi C, Seferovic P, Tavazzi L, Keren A. Classification of the cardiomyopathies: a position statement from the European Society Of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2008; 29:270-276.

[2] Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, Hagege AA, Lafont A, Limongelli G, Mahrholdt H, McKenna WJ, Mogensen J, Nihoyannopoulos P, Nistri S, Pieper PG, Pieske B, Rapezzi C, Rutten FH, Tillmanns C, ns H. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J. 2014 Oct 14;35(39):2733-79. doi: 10.1093/eurheartj/ehu284. Epub 2014 Aug 29. PMID: 25173338

[3] Maron BJ, Rowin EJ, Casey SA, Maron MS. How hypertrophic cardiomyopathy became a contemporary treatable genetic disease with low mortality: shaped by 50 years of clinical research and practice. JAMA Cardiol2016;1:98-105.

[4] Maron BJ, Ommen SR, Semsarian C, Spirito P, Olivotto I, Maron MS. Hypertrophic cardiomyopathy: present and future, with translation into contemporary cardiovascular medicine. J Am Coll Cardiol2014;64:83-99.

[5] Braunwald E, Lambrew CT, Rockoff SD, Ross J Jr, Morrow AG. Idiopathic hypertrophic subaortic stenosis. I. A description of the disease based on an analysis of 64 patients. Circulation 1964;30:Suppl 4: 3-119.

[6] Maron BJ, Maron MS. The remarkable 50 years of imaging in HCM and how it has changed diagnosis and management: from M-mode echocardiography to CMR. JACC Cardiovasc Imaging 2016;9:858-72.

[7] Semsarian C, Ingles J, Maron MS, Maron BJ. New perspectives on the prevalence of hypertrophic cardiomyopathy. J Am Coll Cardiol2015;65:1249-54.

[8] Maron MS, Hellawell JL, Lucove JC, Farzaneh-Far R, Olivotto I. Occurrence of clinically diagnosed hypertrophic cardiomyopathy in the United States. Am J Cardiol2016;117:1651-4.

[9] Wells S, Rowin EJ, Bhatt V, Maron MS, Maron BJ. Association between race and clinical profile of patients referred for hypertrophic cardiomyopathy. Circulation 2018;137:1973-5

[10] Maron BJ. Importance and feasibility of creating hypertrophic cardiomyopathy centers in developing countries: the experience in India. Am J Cardiol 2015;116: 332-4.

[11] 4. Tang B, Song Y, Cui H, et al. Prediction of mid-term outcomes in adult obstructive hypertrophic cardiomyopathy after surgical ventricular septum myectomy. J Am Coll Cardiol2017;70:2092-4.

[12] Greaves SC, Roche AH, Neutze JM, Whitlock RM, Veale AM. Inheritance of hypertrophic cardiomyopathy: a cross sectional and M mode echocardiographic study of 50 families. *Br Heart J*. 1987;58:259-266)

[13] Burke MA, Cook SA, Seidman JG, Seidman CE. Clinical and mechanistic insights into the genetics of cardiomyopathy. J Am Coll Cardiol2016;68:2871-86

[14] Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17:405-24

[15] Ingles J, Burns C, Bagnall RD, et al. Nonfamilial hypertrophic cardiomyopathy: prevalence, natural history, and clinical implications. Circ Cardiovasc Genet. 2017;10:e001620.

[16] Thierfelder L, Watkins H, MacRae C, et al. Alpha-tropomyosin and cardiac tro-ponin T mutations cause familial hyper-trophic cardiomyopathy: a disease of the sarcomere. Cel l 1994;77:701-12.

[17] Valente AM, Lakdawala NK, Powell AJ, et al. Comparison of echocardiographic and cardiac magnetic resonance imaging in hypertrophic cardiomyopathy sarcomere mutation carriers without left ventricular hypertrophy. Circ Cardiovasc Genet 2013; 6:230-7

[18] Landry LG, Rehm HL. Association of racial/ethnic categories with the ability of genetic tests to detect a cause of cardiomyopathy. JAMA Cardiol2018;3:341-5

[19] Ingles J, Burns C, Bagnall RD, et al. Nonfamilial hypertrophic cardiomyopathy: prevalence, natural history, and clinical implications. Circ Cardiovasc Genet 2017; 10:e001620

[20] Chan RH, Maron BJ, Olivotto I, et al. Prognostic value of quantitative contrastenhanced cardiovascular magnetic resonance for the evaluation of sudden death risk in patients with hypertrophic cardiomyopathy. Circulation 2014;130:484-95.

[21] Weng Z, Yao J, Chan RH, et al. Prognostic value of LGE-CMR in HCM: a metaanalysis. JACC Cardiovasc Imaging 2016; 9:1392-402

[22] Spirito P, Bellone P, Harris KM, Bernabò P, Bruzzi P, Maron BJ. Magnitude of left ventricular hypertrophy and risk of sudden death in hypertrophic cardiomyopathy. N Engl J Med 2000;342:1778-85

[23] Klarich KW, AttenhoferJost CH, Binder J, et al. Risk of death in long-term follow-up of patients with apical hypertrophic cardiomyopathy. Am J Cardiol2013;111:1784-91.

[24] Maron MS, Olivotto I, Zenovich AG, et al. Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruction. Circulation 2006;114:2232-9.

[25] Sherrid MV, Balaram S, Kim B, Axel L, Swistel DG. The mitral valve in obstructive hypertrophic cardiomyopathy: a test in context. J Am Coll Cardiol 2016;67: 1846-58.

[26] Maron BJ, Shen W-K, Link MS, et al. Efficacy of implantable cardioverter–defibrillators for the prevention of sudden death in patients with hypertrophic cardiomyopathy. N Engl J Med 2000;342:365-73.

[27] Schinkel AF, Vriesendorp PA, Sijbrands EJ, Jordaens LJ, ten Cate FJ, Michels M. Outcome and complications after implantable cardioverter defibrillator therapy in hypertrophic cardiomyopathy: systematic review and meta-analysis. Circ Heart Fail 2012;5:552-9.

[28] Maron BJ, Maron MS. Contemporary strategies for risk stratification and prevention of sudden death with the implantable defibrillator in hypertrophic cardiomyopathy. Heart Rhythm 2016;13:1155-65.

[29] Vriesendorp PA, Schinkel AF, Van Cleemput J, et al. Implantable

cardioverterdefibrillators in hypertrophic cardiomyopathy: patient outcomes, rate of appropriate and inappropriate interventions, and complications. Am Heart J 2013;166:496-502.

[30] Maron BJ, Spirito P, Shen WK, et al. Implantable cardioverter-defibrillators and prevention of sudden cardiac death in hypertrophic cardiomyopathy. JAMA 2007; 298:405-12.

[31] Maron BJ, Rowin EJ, Casey SA, et al. Hypertrophic cardiomyopathy in adulthood associated with low cardiovascular mortality with contemporary management strategies. J Am Coll Cardiol 2015;65: 1915-28.

[32] Maron BJ, Rowin EJ, Casey SA, et al. Hypertrophic cardiomyopathy in children, adolescents, and young adults associated with low cardiovascular mortality with contemporary management strategies. Circulation 2016;133:62-73.

[33] Maron BJ, Spirito P, Ackerman MJ, et al. Prevention of sudden cardiac death with implantable cardioverter-defibrillators in children and adolescents with hypertrophic cardiomyopathy. J Am Coll Cardiol2013;61:1527-35.

[34] Rowin EJ, Maron BJ, Haas TS, et al. Hypertrophic cardiomyopathy with left ventricular apical aneurysm: implications for risk stratification and management. J Am Coll Cardiol2017;69:761-73

[35] Maron BJ, Udelson JE, Bonow RO, et al. Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: Task Force 3: hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy and other cardiomyopathies, and myocarditis: a scientific statement from the American Heart Association and American College of Cardiology. J Am Coll Cardiol 2015; 66:2362-71.

[36] Maron MS, Rowin EJ, Olivotto I, et al. Contemporary natural history and management of nonobstructive hypertrophic cardiomyopathy. J Am Coll Cardiol 2016; 67:1399-409.

[37] Galati G, Leone O, Pasquale F, et al. Histological and histometric characterization of myocardial fibrosis in end-stage hypertrophic cardiomyopathy: a clinicalpathological study of 30 explanted hearts. Circ Heart Fail 2016;9(9):e003090.

[38] Ho CY, López B, Coelho-Filho OR, et al. Myocardial fibrosis as an early manifestation of hypertrophic cardiomyopathy. N Engl J Med 2010;363:552-63.

[39] Maron BJ, Nishimura RA, Maron MS. Shared decision-making in HCM. Nat Rev Cardiol2017;14:125-6.

[40] Manrai AK, Funke BH, Rehm HL, et al. Genetic misdiagnoses and the potential for health disparities. N Engl J Med 2016; 375:655-65.

[41] Maron BJ, Maron MS, Semsarian C. Genetics of hypertrophic cardiomyopathy after 20 years: clinical perspectives. J Am Coll Cardiol2012;60:705-15.

[42] Biagini E, Olivotto I, Iascone M, et al. Significance of sarcomere gene mutations analysis in the end-stage phase of hypertrophic cardiomyopathy. Am J Cardiol 2014; 114:769-76.

[43] Geske JB, Ong KC, Siontis KC, et al. Women with hypertrophic cardiomyopathy have worse survival. Eur Heart J 2017; 38:3434-40.

[44] Olivotto I, Maron MS, Adabag AS, et al. Gender-related differences in the clinical presentation and outcome of

hypertrophic cardiomyopathy. J Am Coll Cardiol2005;46:480-7.

[45] Rastegar H, Boll G, Rowin EJ, et al. Results of surgical septal myectomy for obstructive hypertrophic cardiomyopathy: the Tufts experience. Ann CardiothoracSurg2017;6:353-63

[46] Ferrazzi P, Spirito P, Iacovoni A, et al. Transaortic chordal cutting: mitral valve repair for obstructive hypertrophic cardiomyopathy with mild septal hypertrophy. J Am Coll Cardiol2015;66:1687-96.

[47] Vriesendorp PA, Liebregts M, Steggerda RC, et al. Long-term outcomes after medical and invasive treatment in patients with hypertrophic cardiomyopathy. JACC Heart Fail 2014;2:630-6

[48] Desai MY, Bhonsale A, Smedira NG, et al. Predictors of long-term outcomes in symptomatic hypertrophic obstructive cardiomyopathy patients undergoing surgical relief of left ventricular outflow tract obstruction. Circulation 2013;128:209-16.

[49] Geske JB, Konecny T, Ommen SR, et al. Surgical myectomy improves pulmonary hypertension in obstructive hypertrophic cardiomyopathy. Eur Heart J 2014;35: 2032-9.

[50] Balaram SK, Ross RE, Sherrid MV, et al. Role of mitral valve plication in the surgical management of hypertrophic cardiomyopathy. Ann ThoracSurg 2012; 94:1990-7.

[51] Rowin EJ, Maron BJ, Olivotto I, Maron MS. Role of exercise testing in hypertrophic cardiomyopathy. JACC Cardiovasc Imaging 2017;10:1374-86.

[52] Valente AM, Lakdawala NK, Powell AJ, et al. Comparison of echocardiographic and cardiac magnetic resonance imaging in hypertrophic cardiomyopathy sarcomere mutation

carriers without left ventricular hypertrophy. Circ Cardiovasc Genet 2013; 6:230-7.

[53] O'Mahony C, Jichi F, Ommen SR, et al. International external validation study of the 2014 European Society of Cardiology Guidelines on Sudden Cardiac Death Prevention in Hypertrophic Cardiomyopathy (EVIDENCE-HCM). Circulation 2018;137: 1015-23.

[54] Maron BJ, Rowin EJ, Casey SA, et al. Risk stratification and outcome of patients with hypertrophic cardiomyopathy ≥60 years of age. Circulation 2013;127: 585-93.

[55] Spirito P, Autore C, Formisano F, et al. Risk of sudden death and outcome in patients with hypertrophic cardiomyopathy with benign presentation and without risk factors. Am J Cardiol2014;113:1550-5.

[56] Kotkar KD, Said SM, Dearani JA, Schaff HV. Hypertrophic obstructive cardiomyopathy: theMayo Clinic experience. Ann CardiothoracSurg2017;6:329-36.

[57] Writing Committee Members, Ommen SR, Mital S, Burke MA, Day SM, Deswal A, Elliott P, Evanovich LL, Hung J, Joglar JA, Kantor P, Kimmelstiel C, Kittleson M, Link MS, Maron MS, Martinez MW, Miyake CY, Schaff HV, Semsarian C, Sorajja P. 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2020 Dec 22;142(25):e558-e631. doi: 10.1161/ CIR.0000000000000937. Epub 2020 Nov 20. Erratum in: Circulation. 2020 Dec 22;142(25):e633. PMID: 33215931.

[58] Smith GA, Dixon HB, Kirschenlohr HL, Grace AA,

Metcalfe JC, Vandenberg JI. Ca2+ buffering in the heart: Ca2+ binding to and activation of cardiac myo-fibrils. Biochem J 2000;346:393-402.

[59] Knollmann BC, Kirchhof P, Sirenko SG, et al. Familial hypertrophic cardiomy-opathy-linked mutant troponin T causes stress-induced ventricular tachycardia and Ca2+−dependent action potential remod-eling. Circ Res 2003;92:428-36.14.

[60] Bers DM, Guo T. Calcium signaling in cardiac ventricular myocytes. Ann N Y Acad Sci 2005;1047:86-98.15.

[61] Huke S, Knollmann BC. Increased myofilament Ca2+−sensitivity and ar-rhythmia susceptibility. J Mol Cell Cardiol2010;48:824-33.16.

[62] Robinson P, Griffiths PJ, Watkins H, Redwood CS. Dilated and hypertrophic cardiomyopathy mutations in troponin and alpha-tropomyosin have opposing ef-fects on the calcium affinity of cardiac thin filaments. Circ Res 2007;101:1266-73

[63] Kampmann C, Wiethoff CM, Wenzel A, Stolz G, Betancor M, Wippermann CF, Huth RG, Habermehl P, Knuf M, Emschermann T, Stopfkuchen H. Normal values of M mode echocardiographic measurements of more than 2000 healthy infants and children in central Europe. Heart 2000;83:667-672

[64] Maron BJ. Distinguishing hypertrophic cardiomyopathy from athlete's heart: a clinical problem of increasing magnitude and significance. Heart 2005;91:1380-2.

[65] Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice

Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2011;58:e212-60.

[66] Li Y, Guo L. Clinical value of carotid wave intensity analysis for differentiating nonobstructive hypertrophic cardiomyopathy from left ventricular hypertrophy secondary to systemic hypertension. J Clin Ultrasound 2013;41:151-7.

[67] Kato TS, Noda A, Izawa H, et al. Discrimination of nonobstructive hypertrophic cardiomyopathy from hypertensive left ventricular hypertrophy on the basis of strain rate imaging by tissue Doppler ultrasonography. Circulation 2004;110:3808-14.

[68] Nagakura T, Takeuchi M, Yoshitani H, et al. Hypertrophic cardiomyopathy is associated with more severe left ventricular dyssynchrony than is hypertensive left ventricular hypertrophy. Echocardiography 2007;24:677-84.

[69] Ogino K, Ogura K, Kinugawa T, et al. Neurohumoral profiles in patients with hypertrophic cardiomyopathy: differences to hypertensive left ventricular hypertrophy. Circ J 2004;68:444-50.

[70] Rapezzi C, Arbustini E, Caforio AL, Charron P, Gimeno-Blanes J, Heliö T, Linhart A, Mogensen J, Pinto Y, Ristic A, Seggewiss H, Sinagra G, Tavazzi L, Elliott PM. Diagnostic work-up in cardiomyopathies: bridging the gap between clinical phenotypes and final diagnosis. A position statement from the ESC Working Group on Myocardial and Pericardial Diseases. Eur Heart J.

2013 May;34(19):1448-58. doi: 10.1093/ eurheartj/ehs397. Epub 2012 Dec 4. PMID: 23211230.

[71] Van der Burgt I. Noonan syndrome. Orphanet J Rare Dis 2007;2:4

[72] Limongelli G, Pacileo G, Marino B, Digilio MC, Sarkozy A, Elliott P, Versacci P, Calabro P, De Zorzi A, Di Salvo G, Syrris P, Patton M, McKenna WJ, Dallapiccola B, Calabro R. Prevalence and clinical significance of cardiovascular abnormalities in patients with the LEOPARD syndrome. Am J Cardiol 2007;100: 736-741.

[73] Vergani V, Lazzeroni D, Peretto G. Bridging the gap between hypertrabeculation phenotype, noncompaction phenotype and left ventricular noncompaction cardiomyopathy. J Cardiovasc Med (Hagerstown). 2020 Mar;21(3):192-199. doi:10.2459/JCM.0000000000000924. PMID: 31895132.

[74] Mehta A, Ricci R, Widmer U, Dehout F, Garcia de Lorenzo A, Kampmann C, Linhart A, Sunder-Plassmann G, Ries M, Beck M. Fabry disease defined: baseline clinical manifestations of 366 patients in the Fabry Outcome Survey. Eur J Clin Invest 2004;34:236-242.

[75] McLeod CJ, Ackerman MJ, Nishimura RA, Tajik AJ, Gersh BJ, Ommen SR. Outcome of patients with hypertrophic cardiomyopathy and a normal electrocardiogram. J Am Coll Cardiol2009;54:229-233.

[76] Monserrat L, Elliott PM, Gimeno JR, Sharma S, Penas-Lado M, McKenna WJ. Nonsustained ventricular tachycardia in hypertrophic cardiomyopathy: an independent marker of sudden death risk in young patients. J Am Coll Cardiol2003;42:873-879. 70.

[77] Adabag AS, Casey SA, Kuskowski MA, Zenovich AG, MaronBJ. Spectrum and prognostic significance of arrhythmias on ambulatory Holter electrocardiogram in hypertrophic cardiomyopathy. J Am Coll Cardiol2005;45:697-704.

[78] Klues HG, Schiffers A, Maron BJ. Phenotypic spectrum and patterns of left ventricular hypertrophy in hypertrophic cardiomyopathy: morphologic observations and significance as assessed by two-dimensional echocardiography in 600 patients. J Am Coll Cardiol1995;26:1699-1708

[79] Cardim N, Galderisi M, Edvardsen T, Plein S, Popescu BA, D'Andrea A, Bruder O, Cosyns B, Davin L, Donal E, Freitas A, Habib G, Kitsiou A, Petersen SE, Schroeder S, Lancellotti P, Camici P, Dulgheru R, Hagendorff A, Lombardi M, Muraru D, Sicari R. Role of multimodality cardiac imaging in the management of patients with hypertrophic cardiomyopathy: an expert consensus of the European Association of Cardiovascular Imaging Endorsed by the Saudi Heart Association. Eur Heart J Cardiovasc Imaging. 2015 Mar;16(3):280. doi: 10.1093/ehjci/jeu291. Epub 2015 Feb 3. PMID: 25650407.

[80] DCiampi Q, Olivotto I, Gardini C, Mori F, Peteiro J, Monserrat L, Fernandez X, Cortigiani L, Rigo F, Lopes LR, Cruz I, Cotrim C, Losi M, Betocchi S, Beleslin B, Tesic M, Dikic AD, Lazzeroni E, Lazzeroni D, Sicari R, Picano E. Prognosticrole of stress echocardiography in hypertrophiccardiomyopathy: The International Stress EchoRegistry. Int J Cardiol. 2016 Sep 15;219:331-8. doi: 10.1016/j.ijcard.2016.06.044. Epub 2016 Jun 15. PMID: 27348413.

[81] O'Hanlon R, Assomull RG, Prasad SK. Use of cardiovascular magnetic resonance for diagnosis and management in hypertrophic cardiomyopathy. CurrCardiol Rep 2007;9:51-56.

[82] O'Gara PT, Bonow RO, Maron BJ, Damske BA, Van Lingen A, Bacharach SL et al. Myocardial perfusion abnormalities in patients with hypertrophic cardiomyopathy: assessment with thallium-201 emission computed tomography. Circulation 1987; 76:1214-23

[83] Shiba N, KagayaY, Ishide N, Otani H, Takeyama D, YamaneYet al. Heterogeneityof myocardial fluoro-18 2-deoxyglucose uptake in patients with apical hypertrophic cardiomyopathy. JpnCirc J 1997;61:223-30.

[84] Schafers MM, Dutka DD, Rhodes CGC, Lammertsma AAA, Hermansen FF, Schober OO et al.Myocardial presynaptic and postsynaptic autonomic dysfunction in hypertrophic cardiomyopathy. Circ Res 1998;82:57-62.

[85] Mehra MR, Kobashigawa J, Starling R, Russell S, Uber PA, Parameshwar J, Mohacsi P, Augustine S, Aaronson K, Barr M. Listing criteria for heart transplantation: International Society for Heart and Lung Transplantation guidelines for the care of cardiac transplant candidates - 2006. J Heart Lung Transplant 2006;25:1024-1042

[86] Elliott PM, Hanna MG, Ward SA, Chinnery PF, Turnbull DM, Wood NW, McKenna WJ. Diagnostic utility of metabolic exercise testing in a patient with cardiovascular disease. Heart 1999;81:441-443. 233.

[87] Sharma S, Elliott P, Whyte G, Jones S, Mahon N, Whipp B, McKenna WJ. Utility of cardiopulmonary exercise in the assessment of clinical determinants of functional capacity in hypertrophic cardiomyopathy. Am J Cardiol2000;86:162-168.

[88] Arena R, Owens DS, Arevalo J, Smith K, Mohiddin SA, McAreavey D, Ulisney KL, Tripodi D, Fananapazir L, Plehn JF. Ventilatoryefficiency and resting hemodynamics in hypertrophic cardiomyopathy. Med Sci Sports Exerc2008;40:799-805.

[89] Sharma S, Elliott PM, Whyte G, Mahon N, Virdee MS, Mist B, McKenna WJ. Utility of metabolic exercise testing in distinguishing hypertrophic cardiomyopathy from physiologic left ventricular hypertrophy in athletes. J Am Coll Cardiol 2000;36: 864-870. 232.

[90] Elliott PM, Hanna MG, Ward SA, Chinnery PF, Turnbull DM, Wood NW, McKenna WJ. Diagnostic utility of metabolic exercise testing in a patient with cardiovascular disease. Heart 1999;81:441-443.

[91] Olivotto I, Cecchi F, Poggesi C, Yacoub MH. Patterns of disease progression in hypertrophic cardiomyopathy: an individualized approach to clinical staging. Circ Heart Fail 2012;5:535-546. 14.

[92] Pasqualucci D, Fornaro A, Castelli G, Rossi A, Arretini A, Chiriatti C, Targetti M, Girolami F, Corda M, Orru P, Matta G, Stefano P, Cecchi F, Porcu M, Olivotto I. Clinical spectrum, therapeutic options, and outcome of advanced heart failure in hypertrophic cardiomyopathy. Circ Heart Fail 2015;8:1014-1021.

[93] Olivotto I, Cecchi F, Poggesi C, Yacoub MH. Patterns of disease progression in hypertrophic cardiomyopathy: an individualized approach to clinical staging. Circ Heart Fail. 2012 Jul 1;5(4):535-46. doi: 10.1161/ CIRCHEARTFAILURE.112.967026. PMID: 22811549.

[94] Olivotto I, Girolami F, Nistri S, Rossi A, Rega L, Garbini F, Grifoni C, Cecchi F, Yacoub MH. The many faces of hypertrophic cardiomyopathy: from developmental biology to clinical

practice. J Cardiovasc Transl Res. 2009;2:349-367.

[95] Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, Naidu SS, Nishimura RA, Ommen SR, Rakowski H, Seidman CE, Towbin JA, Udelson JE, Yancy CW. 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2011;124:2761-2796.

[96] Ho CY. Hypertrophic cardiomyopathy: preclinical and early phenotype. J Cardiovasc Trans Res. 2009;2:462-470

[97] Force T, Bonow RO, Houser SR, Solaro RJ, Hershberger RE, Adhikari B, Anderson ME, Boineau R, Byrne BJ, Cappola TP, Kalluri R, LeWinter MM, Maron MS, Molkentin JD, Ommen SR, RegnierM,TangWH,TianR,KonstamMA, Maron BJ, Seidman CE. Research priorities in hypertrophic cardiomyopathy: report of a Working Group of the National Heart, Lung, and Blood Institute Circulation. 2010;122:1130-1133.

[98] Maron BJ, Maron MS, Wigle ED, Braunwald E. The 50-year history, controversy, and clinical implications of left ventricular outflow tract obstruction in hypertrophic cardiomyopathy: from idiopathic hypertrophic subaortic stenosis to hypertrophic cardiomyopathy. J Am Coll Cardiol. 2009;54:191-200.

[99] Watkins H, Ashrafian H, Redwood C. Inherited cardiomyopathies. N Engl J Med. 2011;364:1643-1656

[100] Spoladore R, Fisicaro A, Faccini A, Camici PG. Coronary microvascular dysfunction in primary cardiomyopathies. Heart. 2014

May;100(10):806-13. doi: 10.1136/ heartjnl-2013-304291. Epub 2013 Jul 31. PMID: 23904360.

[101] Lazzeroni D, Rimoldi O, Camici PG. From Left Ventricular Hypertrophy to Dysfunction and Failure. Circ J. 2016;80(3):555-64. doi: 10.1253/circj.CJ-16-0062. Epub 2016 Feb 5. PMID: 26853555.

[102] Maron BJ, McKenna WJ, Danielson GK, Kappenberger LJ, Kuhn HJ, Seidman CE, Shah PM, Spencer WH III, Spirito P, Ten Cate FJ, Wigle ED. American College of Cardiology/ European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy. J Am Coll Cardiol. 2003;42:1687-1713

[103] Maron BJ, Spirito P. Implications of left ventricular remodeling in hypertrophic cardiomyopathy. Am J Cardiol. 1998;81:1339-1344.

[104] Olivotto I, Maron BJ, Appelbaum E, Harrigan CJ, Salton C, Gibson CM, Udelson JE, O'Donnell C, Lesser JR, Manning WJ, Maron MS. Spectrum and clinical significance of systolic function and myocardial fibrosis assessed by cardiovascular magnetic resonance in hypertrophic cardiomyopathy. Am J Cardiol. 2010;106:261-267.

[105] Yacoub MH, Olivotto I, Cecchi F. 'End–stage' hypertrophic cardiomyopathy: from mystery to model. Nat Clin Pract Cardiovasc Med. 2007;4:232-233.

[106] Olivotto I, Maron BJ, Appelbaum E, Harrigan CJ, Salton C, Gibson CM, Udelson JE, O'Donnell C, Lesser JR, Manning WJ, Maron MS. Spectrum and clinical significance of systolic function and myocardial fibrosis assessed by cardiovascular magnetic resonance in hypertrophic cardiomyopathy. Am J Cardiol. 2010;106:261-267

[107] Biagini E, Spirito P, Rocchi G, Ferlito M, Rosmini S, Lai F, Lorenzini M, Terzi F, Bacchi-Reggiani L, Boriani G, Branzi A, Boni L, Rapezzi C. Prognostic implications of the Doppler restrictive filling pattern in hypertrophic cardiomyopathy. Am J Cardiol. 2009;104:1727-1731.

[108] Melacini P, Basso C, Angelini A, Calore C, Bobbo F, Tokajuk B, Bellini N, Smaniotto G, Zucchetto M, Iliceto S, Thiene G, Maron BJ. Clinicopathological profiles of progressive heart failure in hypertrophic cardiomyopathy. Eur Heart J. 2010;31:2111-2123

[109] Nistri S, Olivotto I, Betocchi S, Losi MA, Valsecchi G, Pinamonti B, Conte MR, Casazza F, Galderisi M, Maron BJ, Cecchi F. Prognostic significance of left atrial size in patients with hypertrophic cardiomyopathy (from the Italian Registry for Hypertrophic Cardiomyopathy). Am J Cardiol. 2006;98:960-965.

[110] Girolami F, Ho CY, Semsarian C, Baldi M, Will ML, Baldini K, Torricelli F, Yeates L, Cecchi F, Ackerman MJ, Olivotto I. Clinical features and outcome of hypertrophic cardiomyopathy associated with triple sarcomere protein gene mutations. J Am Coll Cardiol. 2010;55:1444-1453.

[111] O'Hanlon R, Grasso A, Roughton M, Moon JC, Clark S, Wage R, Webb J, Kulkarni M, Dawson D, Sulaibeekh L, Chandrasekaran B, Bucciarelli-Ducci C, Pasquale F, Cowie MR, McKenna WJ, Sheppard MN, Elliott PM, Pennell DJ, Prasad SK. Prognostic significance of myocardial fibrosis in hypertrophic cardiomyopathy. J Am Coll Cardiol. 2010;56:867-874.

[112] Maron MS, Olivotto I, Maron BJ, Prasad SK, Cecchi F, Udelson JE, Camici PG. The case for myocardial ischemia in hypertrophic cardiomyopathy. J Am Coll Cardiol. 2009;54:866-875.

[113] Olivotto I, Cecchi F, Casey SA, Dolara A, Traverse JH, Maron BJ. Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy. Circulation. 2001;104:2517-2524.

[114] Ciró E, Maron BJ, Bonow RO, Cannon RO, Epstein SE. Relation between marked changes in left ventricular outflow tract gradient and disease progression in hypertrophic cardiomyopathy. Am J Cardiol. 1984;53:1103-1109.

[115] Maron MS, Finley JJ, Bos JM, Hauser TH, Manning WJ, Haas TS, Lesser JR, Udelson JE, Ackerman MJ, Maron BJ. Prevalence, clinical significance and natural history of left ventricular apical aneurysms in hypertrophic cardiomyopathy. Circulation. 2009;118:1541-1549.

[116] Maron MS, Appelbaum E, Harrigan CJ, Buros J, Gibson CM, Hanna C, Lesser JR, Udelson JE, Manning WJ, Maron BJ. Clinical profile and significance of delayed enhancement in hypertrophic cardiomyopathy. Circ Heart Failure. 2008;1:184-191.

[117] Kelly M, Semsarian C. Multiple mutations in genetic cardiovascular disease: a marker of disease severity. Circulation Cardiovasc Genet. 2009;2:182-190.

[118] Biagini E, Coccolo F, Ferlito M, Perugini E, Rocchi G, Bacchi-Reggiani L, Lofiego C, Boriani G, Prandstraller D, Picchio FM, Branzi A, Rapezzi C. Dilated-hypokinetic evolution of hypertrophic cardiomyopathy: prevalence, incidence, risk factors, and prognostic implications in pediatric and adult patients. J Am Coll Cardiol. 2005;46:1543-1550.

[119] Harris KM, Spirito P, Maron MS, Zenovich AG, Formisano F, Lesser JR, Mackey-Bojack S, Manning WJ, Udelson JE, Maron BJ. Prevalence, clinical profile, and significance of left ventricular remodeling in the end-stage

phase of hypertrophic cardiomyopathy. Circulation. 2006;114: 216-225.

[120] Biagini E, Spirito P, Leone O, Picchio FM, Coccolo F, Ragni L, Lofiego C, Grigioni F, Potena L, Rocchi G, Bacchi-Reggiani L, Boriani G, Prandstraller D, Arbustini E, Branzi A, Rapezzi C. Heart transplantation in hypertrophic cardiomyopathy. Am J Cardiol. 2008; 101:387-392.

[121] Kubo T, Gimeno JR, Bahl A, Steffensen U, Steffensen M, Osman E, Thaman R, Mogensen J, Elliott PM, Doi Y, McKenna WJ. Prevalence, clinical significance, and genetic basis of hypertrophic cardiomyopathy with restrictive phenotype. J Am Coll Cardiol. 2007;49:2419-2426

[122] Biagini E, Spirito P, Rocchi G, Ferlito M, Rosmini S, Lai F, Lorenzini M, Terzi F, Bacchi-Reggiani L, Boriani G, Branzi A, Boni L, Rapezzi C. Prognostic implications of the Doppler restrictive filling pattern in hypertrophic cardiomyopathy. Am J Cardiol. 2009;104:1727-1731

[123] Melacini P, Basso C, Angelini A, Calore C, Bobbo F, Tokajuk B, Bellini N, Smaniotto G, Zucchetto M, Iliceto S, Thiene G, Maron BJ. Clinicopathological profiles of progressive heart failure in hypertrophic cardiomyopathy. Eur Heart J. 2010;31:2111-2123.

[124] Day SM. Exercise in hypertrophic cardiomyopathy. J Cardiovasc Transl Res. 2009;2:407-414.

[125] Ammirati E, Contri R, Coppini R, Cecchi F, Frigerio M, Olivotto I. Pharmacological treatment of hypertrophic cardiomyopathy: current practice and novel perspectives. Eur J Heart Fail. 2016 Sep;18(9):1106-18. doi: 10.1002/ejhf.541. Epub 2016 Apr 24. PMID: 27109894.

[126] Stauffer JC, Ruiz V, MorardJD. Subaortic obstruction aftersildenafilina

patient with hypertrophic cardiomyopathy. N Engl J Med 1999;341:700-701

[127] Sherrid MV, Barac I, McKenna WJ, Elliott PM, Dickie S, Chojnowska L, Casey S, Maron BJ. Multicenter study of the efficacy and safety of disopyramide in obstructive hypertrophic cardiomyopathy. J Am Coll Cardiol2005;45:1251-1258.

[128] Sherrid MV, Shetty A, Winson G, Kim B, Musat D, Alviar CL, Homel P, Balaram SK, Swistel DG. Treatment of obstructive hypertrophic cardiomyopathy symptoms and gradient resistant to first-line therapy with beta-blockade or verapamil. Circ Heart Fail 2013;6:694-702.

[129] Adelman AG, Shah PM, Gramiak R, Wigle ED. Long-term propranolol therapy in muscular subaortic stenosis. Br Heart J 1970;32:804-811.

[130] Stenson RE, Flamm MD Jr., Harrison DC, Hancock EW. Hypertrophic subaortic stenosis. Clinical and hemodynamic effects of long-term propranolol therapy. Am J Cardiol1973;31:763-773.

[131] Flamm MD, Harrison DC, HancockEW. Muscular subaortic stenosis. Prevention of outflow obstruction with propranolol. Circulation 1968;38:846-858.

[132] Rosing DR, Kent KM, Borer JS, Seides SF, Maron BJ, Epstein SE. Verapamil therapy: a new approach to the pharmacologic treatment of hypertrophic cardiomyopathy. I. Hemodynamic effects. Circulation 1979;60:1201-1207.

[133] Bonow RO, Rosing DR, Epstein SE. The acute and chronic effects of verapamil on left ventricular function in patients with hypertrophic cardiomyopathy. Eur Heart J 1983;4 Suppl F:57-65.

[134] Spicer RL, Rocchini AP, Crowley DC, Vasiliades J, Rosenthal A. Hemodynamic effectsof verapamil inchildrenandadolescentswith hypertrophiccardiomyopathy. Circulation 1983;67:413-420.

[135] Rosing DR, Idanpaan-Heikkila U, Maron BJ, Bonow RO, Epstein SE. Use of calciumchannel blocking drugs in hypertrophic cardiomyopathy. Am J Cardiol 1985;55: 185B–195B.

[136] Veselka J, Faber L, Liebregts M, Cooper R, Januska J, Kashtanov M, Dabrowski M, Hansen PR, Seggewiss H, Hansvenclova E, Bundgaard H, Ten Berg J, Stables RH, Jensen MK. Short- and long-term outcomes of alcohol septal ablation for hypertrophic obstructive cardiomyopathy in patients with mild left ventricular hypertrophy: a propensity score matching analysis. Eur Heart J 2019;40:1681-1687.

[137] Maron BJ, Nishimura RA. Surgical septal myectomy versus alcohol septal ablation: assessing the status of the controversy in 2014. Circulation 2014;130:1617-1624.

[138] Ten Cate FJ, Soliman OI, Michels M, Theuns DA, de Jong PL, Geleijnse ML, Serruys PW. Long-term outcome of alcohol septal ablation in patients with obstructive hypertrophic cardiomyopathy: a word of caution. Circ Heart Fail 2010;3:362-369

[139] Chan W, Williams L, Kotowycz MA, Woo A, Rakowski H, Schwartz L, Overgaard CB. Angiographic and echocardiographic correlates of suitable septal perforators for alcohol septal ablation in hypertrophic obstructive cardiomyopathy. Can J Cardiol2014;30:912-919.

[140] Sigwart U. Non-surgical myocardial reductionfor hypertrophic obstructivecardiomyopathy. Lancet 1995;346:211-214.

[141] Faber L, Welge D, Fassbender D, Schmidt HK, Horstkotte D, Seggewiss H. One-year follow-up of percutaneous septal ablation for symptomatic hypertrophic obstructive cardiomyopathy in 312 patients: predictors of hemodynamic and clinical response. Clin Res Cardiol2007;96:864-873.

[142] Fernandes VL, Nielsen C, Nagueh SF, Herrin AE, Slifka C, Franklin J, Spencer WH III. Follow-upof alcohol septal ablationfor symptomatic hypertrophic obstructive cardiomyopathy the Baylorand Medical University of South Carolina experience 1996 to 2007. JACC Cardiovasc Interv2008;1:561-570.

[143] Kuhn H, Lawrenz T, Lieder F, Leuner C, Strunk-Mueller C, Obergassel L, Bartelsmeier M, Stellbrink C. Survival after transcoronary ablation of septal hypertrophy in hypertrophic obstructive cardiomyopathy (TASH): a 10 year experience. Clin Res Cardiol2008;97:234-243.

[144] Sorajja P, Valeti U, Nishimura RA, Ommen SR, Rihal CS, Gersh BJ, Hodge DO, Schaff HV, Holmes DR Jr. Outcome of alcohol septal ablation for obstructive hypertrophic cardiomyopathy. Circulation 2008;118:131-139.

[145] Agarwal S, Tuzcu EM, Desai MY, Smedira N, Lever HM, Lytle BW, Kapadia SR. Updated meta-analysis of septal alcohol ablation versus myectomy for hypertrophic cardiomyopathy. J Am Coll Cardiol2010;55:823-834.

[146] Alam M, Dokainish H, Lakkis NM. Hypertrophic obstructive cardiomyopathyalcohol septal ablation vs. myectomy: a meta-analysis. Eur Heart J 2009;30: 1080-1087.

[147] Zeng Z, Wang F, Dou X, Zhang S, Pu J. Comparison of percutaneous

transluminal septal myocardial ablation versus septal myectomy for the treatment of patients with hypertrophic obstructive cardiomyopathy: a meta analysis. Int J Cardiol 2006; 112:80-84.

[148] Leonardi RA, Kransdorf EP, Simel DL, Wang A. Meta-analyses of septal reduction therapies for obstructive hypertrophic cardiomyopathy: comparative rates of overall mortality and sudden cardiac death after treatment. Circ Cardiovasc Interv2010;3:97-104.

[149] Braunwald E, BrockenbroughEC, FryeRL. Studies on digitalis. V. Comparison of the effects of ouabain on left ventricular dynamics in valvular aortic stenosis and hypertrophic subaortic stenosis. Circulation 1962;26:166-173.

[150] Bourmayan C, Razavi A, FournierC, Dussaule JC, Baragan J, Gerbaux A, GayJ. Effect of propranolol on left ventricular relaxation in hypertrophic cardiomyopathy: an echographic study. Am Heart J 1985;109:1311-1316.

[151] Alvares RF, Goodwin JF. Non-invasive assessment of diastolic function in hypertrophic cardiomyopathy on and off beta adrenergic blocking drugs. Br Heart J 1982;48:204-212.

[152] Wilmshurst PT, Thompson DS, Juul SM, Jenkins BS, Webb-Peploe MM. Effects of verapamil on haemodynamic function and myocardial metabolism in patients with hypertrophic cardiomyopathy. Br Heart J 1986;56:544-553.

[153] Udelson JE, Bonow RO, O'Gara PT, Maron BJ, Van Lingen A, Bacharach SL, Epstein SE. Verapamil prevents silent myocardial perfusion abnormalities during exercise in asymptomatic patients with hypertrophic cardiomyopathy. Circulation 1989;79:1052-1060.

[154] Pacileo G, De Cristofaro M, Russo MG, Sarubbi B, Pisacane C, Calabro R. Hypertrophic cardiomyopathy in pediatric patients: effect of verapamil on regional and global left ventricular diastolic function. Can J Cardiol2000;16:146-152.

[155] McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Kober L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Ronnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33:1787-1847.

[156] Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G,Breithardt OA, Cleland J, Deharo JC, Delgado V, Elliott PM, Gorenek B, Israel CW, Leclercq C, Linde C, Mont L, Padeletti L, Sutton R, Vardas PE, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Kirchhof P, Blomstrom-Lundqvist C, Badano LP, Aliyev F, Bansch D, Baumgartner H, Bsata W, Buser P, Charron P, Daubert JC, Dobreanu D, Faerestrand S, Hasdai D, Hoes AW, Le Heuzey JY, Mavrakis H, McDonagh T, Merino JL, Nawar MM, Nielsen JC, Pieske B, Poposka L, Ruschitzka F, Tendera M, Van Gelder IC, Wilson CM. 2013 ESC Guidelines on cardiac pacing and cardiac

resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). Eur Heart J 2013;34:2281-2329.

[157] Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; Authors/ Task Force Members; Document Reviewers. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2016 Aug;18(8):891-975. doi: 10.1002/ejhf.592. Epub 2016 May 20. PMID: 27207191.

[158] Nistri S, Olivotto I, Betocchi S, Losi MA, Valsecchi G, Pinamonti B, Conte MR, Casazza F, Galderisi M, Maron BJ, Cecchi F. Prognostic significance of left atrial size in patients with hypertrophic cardiomyopathy (from the italian registry for hypertrophic cardiomyopathy). Am J Cardiol 2006;98:960-965.

[159] Guttmann OP, Rahman MS, O'Mahony C, Anastasakis A, Elliott PM. Atrial fibrillation and thromboembolism in patients with hypertrophic cardiomyopathy: systematic review. Heart 2014;100:465-472.

[160] Siontis KC, Geske JB, Ong K, Nishimura RA, Ommen SR, Gersh BJ. Atrial fibrillation in hypertrophic cardiomyopathy: Prevalence, clinical correlations, and mortality in a large high-risk population. J Am Heart Assoc 2014;3:e001002.

[161] Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G, KirchhofP. 2012 focused updateof the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J 2012;33:2719-2747.

[162] Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey JY, Ponikowski P, RuttenFH.Guidelinesforthemanagement of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Europace 2010;12: 1360-1420.

[163] Hindricks G, Potpara T, Dagres N, ArbeloE, BaxJJ, Blomström-LundqvistC, Boriani G, Castella M, Dan GA, Dilaveris PE, Fauchier L, Filippatos G, Kalman JM, La Meir M, Lane DA, Lebeau JP, Lettino M, Lip GYH, Pinto FJ, Thomas GN, Valgimigli M, Van Gelder IC, Van Putte BP, Watkins CL; ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2020 Aug 29:ehaa612. doi: 10.1093/ eurheartj/ehaa612. Epub ahead of print. PMID: 32860505.

[164] Elliott PM, Gimeno JR, Thaman R, Shah J, Ward D, Dickie S, Tome Esteban MT, McKenna WJ. Historical trends in reported survival rates in patients with hypertrophic cardiomyopathy. Heart 2006;92:785-791.

[165] Dimitrow PP, Chojnowska L, Rudzinski T, et al. Sudden death in

hypertrophic cardiomyopathy: old risk factors re-assessed in a new model of maximalized follow-up. Eur Heart J. 2010;31:3084-93.

[166] Vriesendorp PA, Schinkel AF, Van Cleemput J, et al. Implantable cardioverter-defibrillators in hypertrophic cardiomyopathy: patient outcomes, rate of appropriate and inappropriate interventions, and complications. Am Heart J. 2013;166:496-502.

[167] Wells S, Rowin EJ, Bhatt V, et al. Association between race and clinical profile of patients referred for hypertrophic cardiomyopathy. Circulation. 2018;137: 1973-5.

[168] Olivotto I, Maron MS, Adabag AS, et al. Genderrelated differences in the clinical presentation and outcome of hypertrophic cardiomyopathy. J Am Coll Cardiol. 2005;46:480-7.

[169] Elliott PM, Poloniecki J, Dickie S, et al. Sudden death in hypertrophic cardiomyopathy: identification of high risk patients. J Am Coll Cardiol. 2000;36:2212-8.

[170] Ostman-Smith I, Wettrell G, Keeton B, et al. Ageand gender-specific mortality rates in childhood hypertrophic cardiomyopathy. Eur Heart J. 2008;29: 1160-7.

[171] Maron BJ. Risk stratification and role of implantable defibrillators for prevention of sudden death in patients with hypertrophic cardiomyopathy. Circulation. 2010;74:2271-82.

[172] Miron A, Lafreniere-Roula M, Fan CS, et al. A validated model for sudden cardiac death risk prediction in pediatric hypertrophic cardiomyopathy. Circulation. 2020;142:217-29.

[173] Norrish G, Ding T, Field E, et al. Development of a novel risk prediction model for sudden cardiac death in childhood hypertrophic cardiomyopathy

(HCM RiskKids). JAMA Cardiol. 2019;4:918-27.

[174] Maron MS, Rowin EJ, Wessler BS, et al. Enhanced American College of Cardiology/American Heart Association strategy for prevention of sudden cardiac death in high-risk patients with hypertrophic cardiomyopathy. JAMA Cardiol. 2019;4:644-57.

[175] Elliott PM, Sharma S, Varnava A, et al. Survival after cardiac arrest or sustained ventricular tachycardia in patients with hypertrophic cardiomyopathy. J Am Coll Cardiol. 1999;33:1596-601.

[176] Bos JM, Maron BJ, Ackerman MJ, et al. Role of family history of sudden death in risk stratification and prevention of sudden death with implantable defibrillators in hypertrophic cardiomyopathy. Am J Cardiol. 2010;106:1481-6.

[177] Spirito P, Bellone P, Harris KM, et al. Magnitude of left ventricular hypertrophy and risk of sudden death in hypertrophic cardiomyopathy. N Engl J Med. 2000; 342:1778-85.

[178] Autore C, Bernabò P, Barillà CS, et al. The prognostic importance of left ventricular outflow obstruction in hypertrophic cardiomyopathy varies in relation to the severity of symptoms. J Am Coll Cardiol. 2005; 45:1076-80.

[179] Elliott PM, Gimeno Blanes JR, Mahon NG, et al. Relation between severity of left-ventricular hypertrophy and prognosis in patients with hypertrophic cardiomyopathy. Lancet. 2001;357:420-4.

[180] Monserrat L, Elliott PM, Gimeno JR, et al. Nonsustained ventricular tachycardia in hypertrophic cardiomyopathy: an independent marker of sudden death risk in young patients. J Am Coll Cardiol. 2003;42:873-9.

[181] Wang W, Lian Z, Rowin EJ, et al. Prognostic implications of nonstained ventricular tachycardia in high-risk patients with hypertrophic cardiomyopathy. CircArrhythmElectrophysiol. 2017;10:e004604.

[182] Corona-Villalobos CP, Sorensen LL, Pozios I, et al. Left ventricular wall thickness in patients with hypertrophic cardiomyopathy: a comparison between cardiac magnetic resonance imaging and echocardiography. Int J Cardiovasc Imaging. 2016;32: 945-54.

[183] Bois JP, Geske JB, Foley TA, et al. Comparison of maximal wall thickness in hypertrophic cardiomyopathy differs between magnetic resonance imaging and transthoracic echocardiography. Am J Cardiol. 2017; 119:643-50.

[184] Maron MS, Lesser JR, Maron BJ. Management implications of massive left ventricular hypertrophy in hypertrophic cardiomyopathy significantly underestimated by echocardiography but identified by cardiovascular magnetic resonance. Am J Cardiol. 2010;105:1842-3.

[185] Weng Z, Yao J, Chan RH, et al. Prognostic value of LGE-CMR in HCM: a meta-analysis. J Am Coll CardiolImg. 2016;9:1392-402. 19. Chan RH, Maron BJ, Olivotto I, et al. Prognostic value of quantitative contrast-enhanced cardiovascular magnetic resonance for the evaluation of sudden death risk in patients with hypertrophic cardiomyopathy. Circulation. 2014;130:484-95.

[186] Mentias A, Raeisi-Giglou P, Smedira NG, et al. Late gadolinium enhancement in patients with hypertrophic cardiomyopathy and preserved systolic function. J Am Coll Cardiol. 2018;72:857-70.

[187] Maron BJ, Rowin EJ, Casey SA, et al. Hypertrophic cardiomyopathy in adulthood associated with low cardiovascular mortality with contemporary management strategies. J Am Coll Cardiol. 2015;65:1915-28. 32. Maron BJ, Rowin EJ, Casey SA, et al. Risk stratification and outcome of patients with hypertrophic cardiomyopathy $60 years of age. Circulation. 2013; 127:585-93.

[188] Spudich JA. Three perspectives on the molecular basis of hypercontractility caused by hypertrophic cardiomyopathy mutations. Pflugers Arch 2019;471:701-717.

[189] Spudich JA, Aksel T, Bartholomew SR, Nag S, Kawana M, Yu EC, Sarkar SS, Sung J, Sommese RF, Sutton S, Cho C, Adhikari AS, Taylor R, Liu C, Trivedi D, Ruppel KM. Effects of hypertrophic and dilated cardiomyopathy mutations on power output by human beta-cardiac myosin. J Exp Biol 2016;219(Pt 2):161-167

[190] Frey N, Luedde M, Katus HA. Mechanisms of disease: hypertrophic cardiomyopathy. Nat Rev Cardiol2011;9:91-100.

[191] Toepfer CN, Wakimoto H, Garfinkel AC, McDonough B, Liao D, Jiang J, Tai AC, Gorham JM, Lunde IG, Lun M, Lynch TL, McNamara JW, Sadayappan S, Redwood CS, Watkins HC, Seidman JG, Seidman CE. Hypertrophic cardiomyopathy mutations in MYBPC3 dysregulate myosin. Sci Transl Med 2019;11:eaat1199

[192] Olivotto I, Oreziak A, Barriales-Villa R, Abraham TP, Masri A, Garcia-Pavia P, Saberi S, Lakdawala NK, Wheeler MT, Owens A, Kubanek M, Wojakowski W, Jensen MK, Gimeno-Blanes J, Afshar K, Myers J, Hegde SM, Solomon SD, Sehnert AJ, ZhangD,LiW,BhattacharyaM,EdelbergJM, Waldman CB, Lester SJ, Wang A, Ho CY, Jacoby D; EXPLORER-HCM study investigators. Mavacamten for treatment of symptomatic obstructive

hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2020 Sep 12;396(10253):759-769. doi: 10.1016/S0140-6736(20)31792-X. Epub 2020 Aug 29. Erratum in: Lancet. 2020 Sep 12;396(10253):758. PMID: 32871100.

[193] Coppini R, Ferrantini C, Yao L, Fan P, Del Lungo M, Stillitano F, Sartiani L, Tosi B, Suffredini S, Tesi C, Yacoub M, Olivotto I, Belardinelli L, Poggesi C, Cerbai E, Mugelli A. Late sodium current inhibition reverses electromechanical dysfunction in human hypertrophic cardiomyopathy. Circulation 2013;127:575-584.

[194] Olivotto I, Camici PG, Merlini PA, Rapezzi C, Patten M, Climent V, Sinagra G, Tomberli B, Marin F, Ehlermann P, Maier LS, Fornaro A, Jacobshagen C, Ganau A, Moretti L, Hernandez Madrid A, Coppini R, Reggiardo G, Poggesi C, Fattirolli F, Belardinelli L, Gensini G, Mugelli A. Efficacy of ranolazine in patients with symptomatic hypertrophic cardiomyopathy: the RESTYLE-HCM randomized, double-blind, placebo-controlled study. Circ Heart Fail 2018;11:e004124.

[195] Shimada YJ, Passeri JJ, Baggish AL, O'Callaghan C, Lowry PA, Yannekis G, Abbara S, Ghoshhajra BB, Rothman RD, Ho CY, Januzzi JL, Seidman CE, Fifer MA. Effects of losartan on left ventricular hypertrophy and fibrosis in patients with nonobstructive hypertrophic cardiomyopathy. JACC Heart Fail 2013;1:480-487.

[196] Axelsson A, Iversen K, Vejlstrup N, Ho C, Norsk J, Langhoff L, Ahtarovski K, Corell P, Havndrup O, Jensen M, Bundgaard H. Efficacy and safety of the angiotensin II receptor blocker losartan for hypertrophic cardiomyopathy: the INHERIT randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol 2015;3:123-131.

[197] Maron MS, Chan RH, Kapur NK, Jaffe IZ, McGraw AP, Kerur R, Maron BJ, Udelson JE. Effect of spironolactone on myocardial fibrosis and other clinical variables in patients with hypertrophic cardiomyopathy. Am J Med 2018;131:837-841.

[198] Axelsson A, Iversen K, Vejlstrup N, Ho CY, Havndrup O, Kofoed KF, Norsk J, Jensen M, Bundgaard H. Functional effects of losartan in hypertrophic cardiomyopathy – a randomised clinical trial. Heart 2016;102:285-291.

[199] Senthil V, Chen SN, Tsybouleva N, Halder T, Nagueh SF, Willerson JT, Roberts R, Marian AJ. Prevention of cardiac hypertrophy by atorvastatin in a transgenic rabbit model of human hypertrophic cardiomyopathy. Circ Res 2005;97:285-292.

[200] Nagueh SF, Lombardi R, Tan Y, Wang J, Willerson JT, Marian AJ. Atorvastatin and cardiac hypertrophy and function in hypertrophic cardiomyopathy: a pilot study. Eur J Clin Invest 2010;40:976-983.

[201] Musunuru K. Genome editing: the recent history and perspective in cardiovascular diseases. J Am Coll Cardiol2017;70:2808-2821.

[202] German DM, Mitalipov S, Mishra A, Kaul S. Therapeutic genome editing in cardiovascular diseases. JACC Basic Transl Sci 2019;4:122-131.

[203] Strong A, Musunuru K. Genome editing in cardiovascular diseases. Nat Rev Cardiol2017;14:11-20.

[204] Ma H, Marti-Gutierrez N, Park SW, Wu J, Lee Y, Suzuki K, Koski A, Ji D, Hayama T, Ahmed R, Darby H, Van Dyken C, Li Y, Kang E, Park AR, Kim D,

Kim ST, Gong J, Gu Y, Xu X, Battaglia D, Krieg SA, Lee DM, Wu DH, Wolf DP, Heitner SB, Belmonte JCI, Amato P, Kim JS, Kaul S, Mitalipov S. Correction of a pathogenic gene mutation in human embryos. Nature 2017;548:413-419.

[205] Bongianino R, Denegri M, Mazzanti A, Lodola F, Vollero A, Boncompagni S, Fasciano S, Rizzo G, Mangione D, Barbaro S, Di Fonso A, Napolitano C, Auricchio A, Protasi F, Priori SG. Allele-specific silencing of mutant mRNA rescues ultrastructural and arrhythmic phenotype in mice carriers of the R4496C mutation in the ryanodine receptor gene (RYR2). Circ Res 2017;121: 525-536

[206] Jiang J, Wakimoto H, Seidman JG, Seidman CE. Allele-specific silencing of mutant MYH6 transcripts in mice suppresses hypertrophic cardiomyopathy. Science 2013;342:111-114.

[207] Zaleta-Rivera K, Dainis A, Ribeiro AJS, Cordero P, Rubio G, Shang C, Liu J, Finsterbach T, Parikh VN, Sutton S, Seo K, Sinha N, Jain N, Huang Y, Hajjar RJ, Kay MA, Szczesna-Cordary D, Pruitt BL, Wheeler MT, Ashley EA. Allele-specific silencing ameliorates restrictive cardiomyopathy attributable to a human myosin regulatory light chain mutation. Circulation 2019;140:765-778.