Heart Failure Reviews (2019) 24:439–459
https://doi.org/10.1007/s10741-019-09775-4

Hypertrophic cardiomyopathy: an updated review on diagnosis, prognosis, and treatment

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Published online: 9 March 2019

Abstract
Hypertrophic cardiomyopathy (HCM) represents a phenotype of left ventricular hypertrophy unexplained by abnormal loading conditions. The definition is based on clinical criteria; however, there are numerous underlying etiologic factors. The MOGE(S) classification provides a standardized approach for multimodal characterization of HCM. HCM is associated with increased morbidity and mortality, and especially the assessment of the risk of sudden cardiac death is of paramount importance. In this review, we summarize essential knowledge and recently published data on clinical presentation, diagnosis, genetic analyses, differential diagnosis, prognosis, and treatment options that are necessary for understanding and management of HCM.

Keywords Hypertrophic cardiomyopathy · Etiology · Diagnosis · Treatment

Abbreviations

ASA	Alcohol septal ablation
CMR	Cardiac magnetic resonance
CT	Computed tomography
CAD	Coronary artery disease
ECV	Extracellular volume
HCM	Hypertrophic cardiomyopathy
HOCM	Hypertrophic obstructive cardiomyopathy
LA	Left atrial
LGE	Late gadolinium enhancement
LV	Left ventricular
LVEF	Left ventricular ejection fraction
LVOT	Left ventricular outflow tract
SAM	Systolic anterior motion
TDI	Tissue Doppler imaging
TEE	Transesophageal echocardiography

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Definition and etiology

Hypertrophic cardiomyopathy (HCM) is characterized by the presence of increased left ventricular (LV) wall thickness that is not solely explained by abnormal loading conditions such as hypertension or valvulopathies [1, 2]. Left ventricular hypertrophy is typically severe and asymmetric, mainly affecting the interventricular septum. However, asymmetric hypertrophy is not specific of HCM, as it may also be observed in hypertensive cardiomyopathy and isolated basal hypertrophy of the interventricular septum [2].

In up to 60% of HCM in adults, the disease is caused by mutations of the cardiac sarcomere protein genes and involve an autosomal dominant pattern of inheritance [3, 4]. The most common mutations are related to genes encoding heavy chains of b myosin (MYH7) and myosin-binding protein C (MYBPC3) whereas genes related to cardiac troponin I and T (TNNI3, TNNT2), tropomyosin alpha-1 chain (TPM1), and myosin light chain 3 (MYL3) are less commonly involved [2]. Presence of sarcomere protein mutation is associated with

more severe hypertrophy, myocardial fibrosis, and increased prevalence of sudden cardiac death (SCD) [5, 6].

In 5–10% of patients, there are other genetic disorders including metabolic (Danon disease, Anderson–Fabry disease, ATP-kinase-PRKA G2) [7, 8] and neuromuscular (Friedreich's ataxia) [9] diseases, mitochondrial diseases, and malformation syndromes, whereas in 25–30% of the cases, HCM is of unknown etiology (sporadic cases). A specific case is amyloidosis including hereditary transthyretin (TTR)-related amyloidosis, AL, and senile amyloidosis that resemble genetic forms of HCM [10].

For a standardized diagnostic workup and classification of cardiomyopathies, including HCM, the MOGE(S) classification has been introduced, based on five attributes, including morphofunctional characteristics (M), organ involvement (O), genetic or familial inheritance pattern (G), etiological annotation (E), and optional information about the heart failure functional status (S) [11].

Diagnostic workup

Typical HCM symptoms include dyspnea, palpitations, chest pain, exercise intolerance, and syncope. A systolic ejection murmur best heard between the apex and the left sternal border, of increasing intensity with maneuvers that decrease preload or afterload, can raise the suspicion of the presence of LV outflow tract (LVOT) obstruction.

In adults, 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 [CMR] imaging or computed tomography [CT]) [2].

Electrocardiogram

Electrocardiogram (ECG) is a valuable diagnostic tool for the detection of HCM as it may demonstrate LV hypertrophy, ST/T wave abnormalities, or pathological Q waves and lead to further testing (echocardiography or CMR). It is recommended to be combined with 48-h Holter rhythm monitoring for the assessment of the risk of SCD or stroke by the detection of ventricular or atrial arrhythmias (most often atrial fibrillation) respectively. The ECG is a sensitive marker of HCM and may precede echocardiographic findings of the disease. That means that the subject may carry the responsible mutation (pathological genotype) but the disease has not been clinically manifested yet (normal phenotype), thus implying the need for regular monitoring.

ECG findings suggestive of specific HCM morphological variants include [2, 12]:

(1) LV hypertrophy positive criteria (Sokolow–Lyon index).
(2) Pathological Q waves in the inferior-lateral leads with ≥ 40 ms duration and ≥ 3 mm depth in combination with positive T waves suggest LV asymmetric hypertrophy and areas of myocardial fibrosis.
(3) Giant (> 10 mm) negative T waves in precordial and/or inferior leads suggest HCM of the LV apex.
(4) ST segment elevation in precordial or lateral leads in the absence of anterior wall myocardial infarction suggests the presence of LV apex aneurysm.
(5) Atrioventricular block is associated with Anderson–Fabry, amyloidosis, and PRKAG2 mutations.
(6) Low-voltage QRS complexes in the absence of obesity, emphysema, and pericardial effusion are associated with amyloidosis.
(7) Pre-excitation syndrome is observed in Danon's disease and PRKAG2 mutation. A short PR interval without pre-excitation is described in Anderson–Fabry.

Echocardiography

The main imaging findings in HCM are summarized in Table 1. Echocardiography has a central role in the diagnosis and monitoring of HCM patients. Most patients have an asymmetric LV hypertrophy affecting mainly the interventricular septum (Fig. 1a), whereas other patterns of hypertrophy including concentric (Fig. 1b), apical (Fig. 1c), midventricular (Fig. 2), or of the anterolateral or inferior wall are less common and often more challenging to be diagnosed [28].

The thickness of all LV segments, from base to apex, should be measured by echocardiography. Measurements are taken preferably in parasternal short axis views with orthogonal beam alignment in order to avoid oblique orientation leading to wall thickness overestimation. In case of apical hypertrophy, additional apical views are important for the assessment of hypertrophy of the apical segments. It is recommended to avoid measurements from the apical views, due to possible overestimation of the thickness of the LV walls [2].

In cases of inadequate visualization of a segment, the use of contrast agents for optimal LV opacification and/or CMR should be considered. Particular attention should be paid for the thorough investigation of LV apex for the detection of apical hypertrophy or apical aneurysm (Fig. 2).

About one third of HCM patients present with LVOT obstruction at rest, mainly due to systolic anterior motion of the mitral valve (SAM). Systolic anterior motion can be detected with two-dimensional (Fig. 3a). and M-echocardiography (Fig. 3b). Severe interventricular septum hypertrophy, mitral leaflet abnormalities, papillary muscle hypertrophy, and displacement may also contribute to intracavitary obstruction. Another one third of HCM patients have latent LVOT obstruction provoked by a decrease in preload and/or afterload or an increase in LV contractility [13]. In everyday clinical practice, the Valsalva maneuver (exhale with

Table 1 Imaging assessment in hypertrophic cardiomyopathy (ref. [2, 13–27])

Echocardiography

LV hypertrophy

Unexplained LV wall thickness ≥ 15 mm in one or more myocardial segments

- Asymmetric/interventricular septum
- Concentric
- Apical
- Midventricular
- Anterolateral or inferior wall

Intracavitary obstruction

Pressure gradient ≥ 30 mmHg at rest or provoked

- LVOT obstruction
  - SAM
  - Severe interventricular septum hypertrophy
  - Mitral leaflet abnormalities
  - Papillary muscle hypertrophy and displacement
- Midventricular obstruction
  - Severe midwall hypertrophy
  - Apical aneurysms and thrombi

Systolic function

- LVEF preserved/reduced in burn-out phenotype
- Impaired GLS particularly in hypertrophic LV segments

Diastolic function

Findings consistent with diastolic dysfunction

- *E*/*e*′ average > 14
- LA volume index > 34 mL/m^2
- Peak TR velocity > 2.8 m/s
- Reduced myocardial velocities by TDI septal < 7 cm/s, lateral < 10 cm/s

Mitral valve

- SAM
- Mitral regurgitation jet eccentric/central
- Endogenous mitral valve abnormalities
  - Leaflet prolapse
  - Elongated mitral leaflets
  - Elongation and anomalous insertion of chords
  - Papillary muscle abnormalities

Left atrium

Anteroposterior diameter

LA indexed volume

Exercise echo

- Provocation of latent LVOT obstruction
- Response of blood pressure to exercise
- Induction of ventricular arrhythmias

Cardiac MRI

- LV wall thickness in poorly visualized segments by echocardiography
  - LV apex
  - Anterolateral wall
  - Apical aneurysms and thrombi
- Papillary muscle abnormalities
- Myocardial crypts
- Tissue characterization
  - Presence and extent of myocardial fibrosis by LGE
  - Extracellular volume by T1 mapping
- Systolic function
  LV and RV volumes, ejection fraction

Table 1 (continued)

Positron emission tomography (PET)
Assessment of myocardial ischemia and microcirculatory dysfunction
CT coronary angiography
Epicardial coronary artery obstructive lesions
Intramuscular cardiac course of arteries

LV left ventricular, *LVOT* left ventricular outflow tract, *SAM* systolic anterior motion, *LVEF* left ventricular ejection fraction, *GLS* global longitudinal strain, *LA* left atrium, *TR* tricuspid regurgitation, *TDI* tissue Doppler imaging, *MRI* magnetic resonance imaging, *LGE* late gadolinium enhancement, *RV* right ventricular, *CT* computed tomography

closed glottis) or the administration of nitrates is used for the provocation of LV obstruction in HCM. An upright exercise test is slightly more sensitive than the Valsalva maneuver [14]. LVOT obstruction is defined as a Doppler-derived peak instantaneous LVOT pressure gradient ≥ 30 mmHg, typically with a late-peaking profile (Fig. 3d), either at rest or during Valsalva maneuver or exercise. Therefore, the baseline measurements should be matched with dynamic measurements. Typically, SAM is associated with mitral regurgitation (Fig. 3c) and with an eccentric, inferolaterally directed jet. A centrally directed mitral regurgitation jet is usually associated with endogenous mitral valve abnormalities; thus, further assessment of the mitral anatomy with transesophageal echocardiography (TEE) is necessary [2, 13].

Particular attention should be paid to other causes of elevated pressure gradients within the left ventricle unrelated to SAM, including midventricular hypertrophy with midventricular obstruction, subaortic membranes, or aortic stenosis. In such cases, the assessment of LVOT obstruction or aortic stenosis severity becomes challenging.

LV midcavity obstruction represents approximately 10% of HCM patients [15]. Patients with midcavity obstruction are often highly symptomatic and seem to have increased risk of heart failure and SCD [29]. Approximately 25% of those patients also have LV apical aneurysm which seems to be linked with thrombi formation within the aneurysm [16], increased risk for monomorphic ventricular tachycardia due to apical scarring [30], and increased cardiovascular mortality [15, 29].

The LV ejection fraction (LVEF) in HCM is usually preserved or even increased due to increased radial thickening; however, the LVEF is not a reliable parameter of systolic function in the presence of LV hypertrophy [17]. Additionally, the stroke volume may be reduced due to the small LV cavity. Valuable information regarding the assessment of LV systolic function is provided by new echocardiographic techniques such as speckle tracking echocardiography. Longitudinal deformation is impaired in hypertrophic segments (Fig. 4). In the early stages of the disease, the longitudinal strain may be reduced even in the presence of normal EF and before the development of hypertrophy in relatives of HCM patients [18, 19].

In advanced stages of the disease 5–10% of patients with HCM develop a “burnt-out” phenotype with regression of

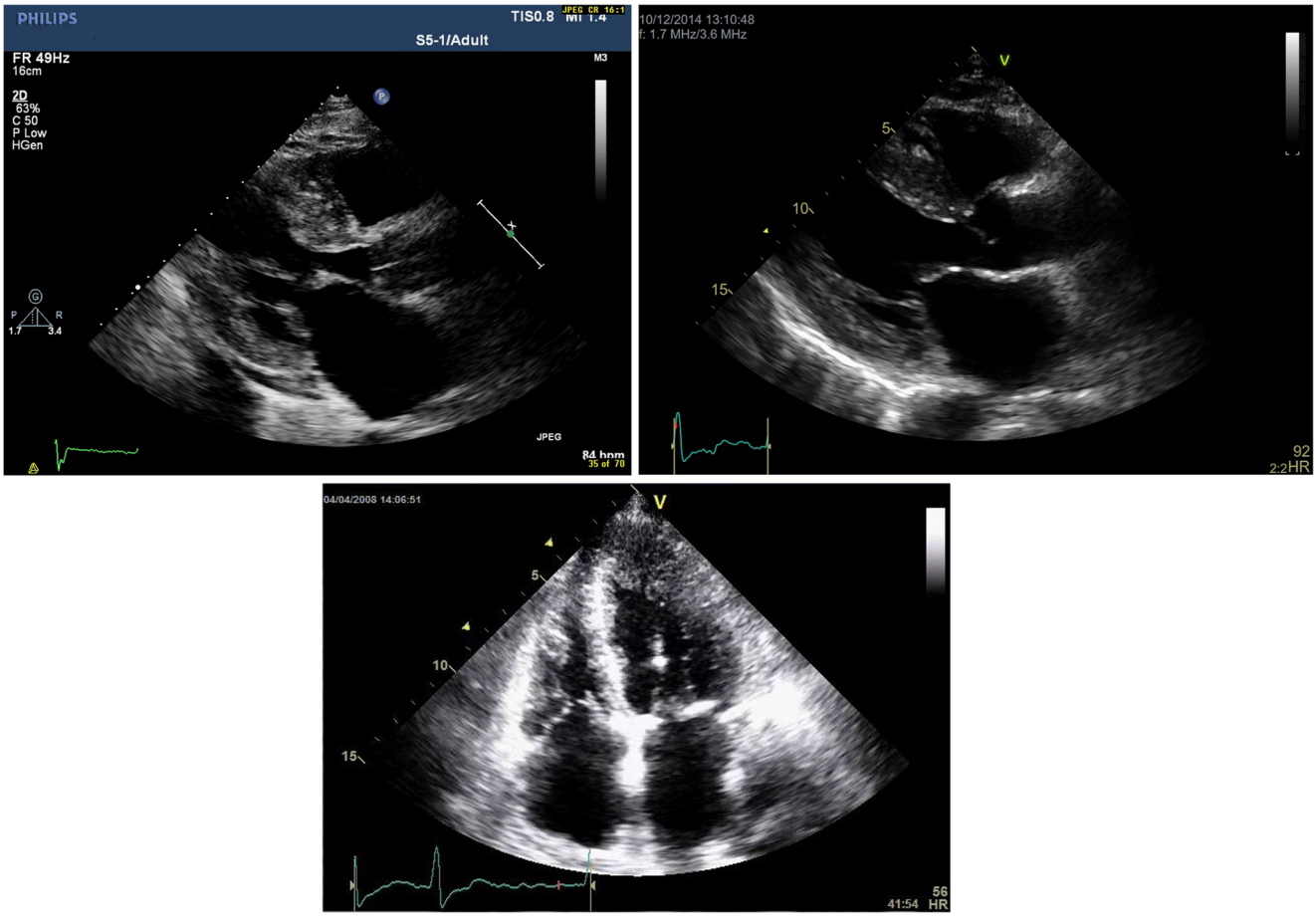

Fig. 1 Asymmetric hypertrophy of the interventricular septum (**a**) and concentric (**b**) and apical (**c**) LV hypertrophy

hypertrophy, LV dilation, and decrease in LVEF [31]. LVEF < 50% is indicative of advanced systolic dysfunction and is often accompanied by rapid clinical deterioration [2, 17]. Microvascular dysfunction leading to diffuse myocardial ischemia, myocardial cell death, and fibrosis may represent the main underlying mechanism [32].

It has recently been indicated that global longitudinal strain (GLS) has a prognostic value in HCM: Patients with a GLS

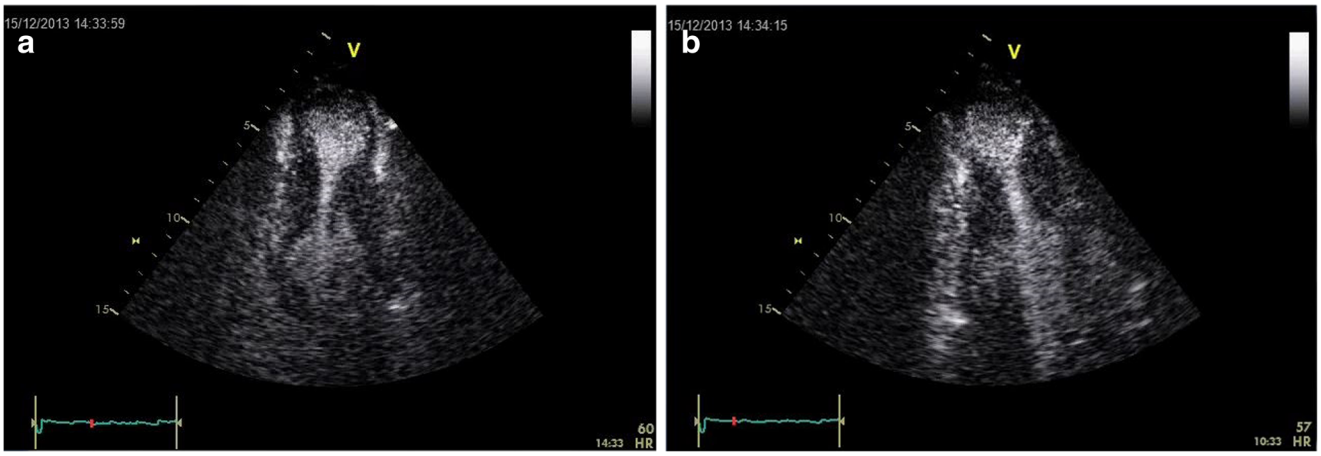

Fig. 2 Contrast echocardiography: four-chamber (**a**) and two-chamber (**b**) views of midventricular hypertrophy with apical aneurysm and thrombus formation within the aneurysm

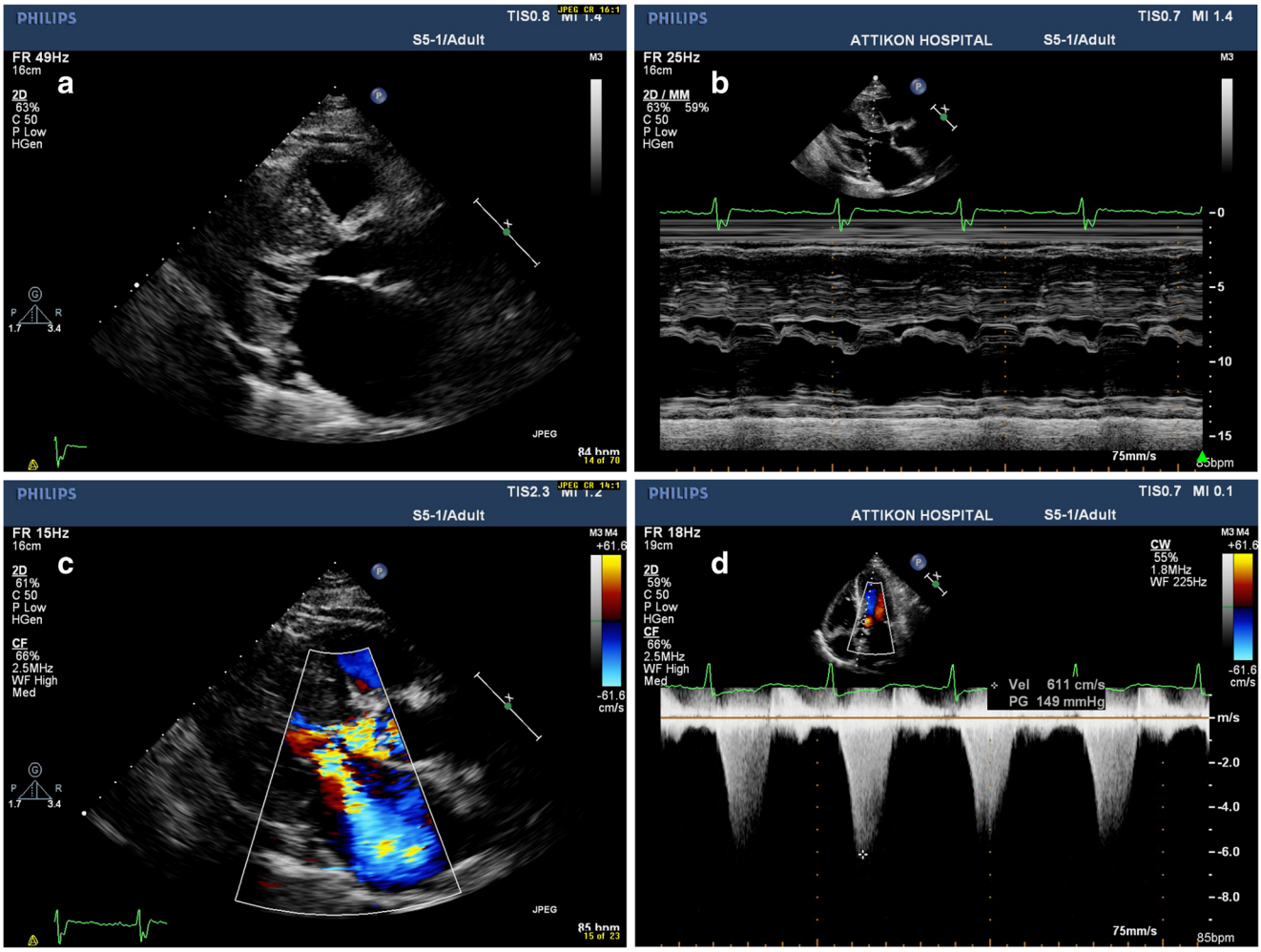

Fig. 3 Systolic anterior motion (SAM) of the mitral valve with 2D (**a**) and m-mode (**b**) causing LVOT obstruction and SAM-associated MR (**c**). A max instantaneous late peak gradient of 149 mmHg was measured with CW Doppler (**d**), indicative of severe LVOT obstruction

value > − 16% had adverse prognosis with significantly higher risk for new-onset sustained ventricular tachycardia/fibrillation, heart failure, cardiac transplantation, and all-cause death compared to patients with GLS < − 16% in a 3-year follow-up period. Moreover, a GLS value > − 10% had four times higher risk of events compared with GLS ≤ − 16% ($p = 0.006$) [20].

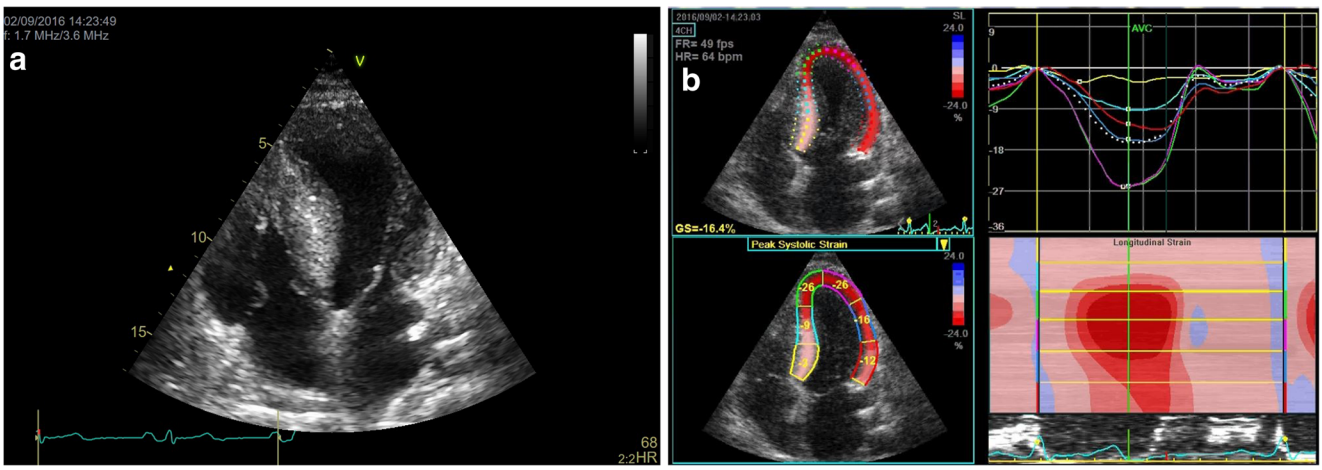

Fig. 4 Hypertrophic cardiomyopathy with asymmetric hypertrophy of the interventricular septum (**a**) and impaired longitudinal strain − 16.4% particularly in the basal and midseptum segments (**b**)

Table 2 Differential diagnosis of LV hypertrophy (ref. [2, 12, 25, 33–55])

	Hypertrophic cardiomyopathy	Athlete's heart	Hypertensive heart disease	Cardiac amyloidosis	Anderson–Fabry disease	Isolated basal hypertrophy of the IVS
ECG	"Particularly pathological" ECG pattern with LV hypertrophy ST/T wave abnormalities profound T wave inversion pathological Q waves	High QRS voltage, sinus bradycardia, first-degree, Mobitz I atrioventricular block, early repolarization with ST elevation, ST elevation with T wave inversion in V1–V4. T wave inversion in V1–V4 in children < 16 years old Incomplete RBBB, ectopic atrial or junctional rhythm.	LV hypertrophy, marked repolarization abnormalities, and unusual Q waves	Low QRS voltages (AL amyloidosis)	LV hypertrophy, shortened P wave duration, shortened or prolonged PQ interval, shortened QRS duration, prolonged QT interval atrioventricular conduction abnormalities	Not specific findings, may show LV hypertrophy
Echo						
Left ventricle	• Unusual pattern of severe (≥ 15 mm) LV hypertrophy - asymmetric - apical - midventricular • LV end-diastolic diameter < 45 mm • LVOT obstruction with SAM in 30% of HCM at rest • Impaired GLS specifically in hypertrophic segments	• Mild to moderate (< 15 mm) LV hypertrophy - concentric • Enlarged LV > 55 mm end-diastolic diameter • No LV obstruction • Normal GLS	• Mild to moderate (< 15 mm) LV hypertrophy - concentric	• Moderately increased LV wall thickness - Concentric • Sparkling myocardium • Apical sparing of longitudinal strain	• Concentric LVH Inferolateral hypokinesia • Basal/inferolateral hypokinesia	• IVS thickness < 15 mm at basal segment in combination with posterior wall thickness < 11 mm • Absence of SAM and LVOT obstruction at rest
Right ventricle	• Increased RV free wall thickness	• Enlarged RV	• No specific RV abnormalities	• Increased RV free wall thickness	• Increased RV free wall thickness	• No specific RV abnormalities
Diastolic function	• Diastolic dysfunction, abnormal values for tissue Doppler myocardial velocities	• Normal diastolic function, normal values for tissue Doppler myocardial velocities	• Diastolic dysfunction, abnormal values for tissue Doppler myocardial velocities	• Diastolic dysfunction, abnormal values for tissue Doppler myocardial velocities	• Diastolic dysfunction, abnormal values for tissue Doppler myocardial velocities	
Atria	• Enlarged left atrium	• Usually normal LA size	• Usually enlarged LA	• Biatrial enlargement, increased IAS thickness	• Enlarged LA	
Valves	• Mitral valve and papillary muscle abnormalities, mitral regurgitation	• No specific abnormalities	• No specific abnormalities	• Thickened atrioventricular cardiac valves and papillary muscles	• Thickened atrioventricular cardiac valves	
Other features	• No regression of LV hypertrophy after a period of deconditioning • Regression of LV hypertrophy and impaired LVEF in "burnt-out" phenotype	• Regression of LV thickness and mass after a period of deconditioning	• Possible regression of LVH after antihypertensive treatment	• No regression of LV thickness • Pericardial effusion	• Regression of hypertrophy after α-galactosidase replacement therapy	• No regression of basal IVS hypertrophy
Cardiac MRI	• Extensive LGE areas with midwall patchy enhancement • Increased ECV by T1 mapping	• No LGE areas • Reduction in ECV as "hypertrophy" increases	• Extensive LGE areas unusual	• LGE pattern of distribution with diffuse subendocardial or transmural enhancement	• LGE in the basal inferolateral wall	• Absence of LGE at basal IVS

Table 2 (continued)

	Hypertrophic cardiomyopathy	Athlete's heart	Hypertensive heart disease	Cardiac amyloidosis	Anderson–Fabry disease	Isolated basal hypertrophy of the IVS
Other tests	Mutations compatible with HCM in genetic testing, family history of HCM	No specific abnormalities	History of hypertension	in combination with dark blood pool, 99mTc-3,3-diphosphono-1,2 propanodicarboxylic acid (bone) scintigraphy uptake in TTR-associated amyloidosis	α-Galactosidase deficiency	No mutations compatible with HCM in genetic testing, no family history of HCM, no typical symptoms of HCM

IVS interventricular septum, *LV* left ventricular, *LVOT* left ventricular outflow tract, *SAM* systolic anterior motion, *HCM* hypertrophic cardiomyopathy, *GLS* global longitudinal strain, *LVEF* left ventricular ejection fraction, *LVH* left ventricular hypertrophy, *LA* left atrium, *IAS* interatrial septum, *MRI* magnetic resonance imaging, *LGE* late gadolinium enhancement, *RV* right ventricular, *TTR* transthyretin

HCM is usually characterized by the presence of diastolic dysfunction (Tables 1, 2). The restrictive pattern of diastolic dysfunction, $E/A > 2$, and E deceleration time < 150 ms is associated with an adverse prognosis [56]. Additionally, a ratio E/e' average > 14, left atrial (LA) volume index > 34 mL/m^2, peak velocity of tricuspid regurgitation (TR) jet > 2.8 m/s, and reduced myocardial velocities by tissue Doppler imaging (TDI) septal < 7 cm/s and lateral < 10 cm/s are parameters consistent with the presence of diastolic dysfunction and raised LV filling pressures [21]. A higher E/e' has been proposed as a prognostic factor of worse event-free survival in nonobstructive HCM patients and in patients with residual obstruction after myectomy [57].

The left atrium is often enlarged in patients with HCM due to SAM-related mitral regurgitation and elevated LV filling pressures.

Although the anteroposterior LA diameter has been widely used for the prediction of embolic events and SCD in HCM [58, 59], left atrial volume indexed to body surface area provides a more accurate assessment of LA enlargement in case of asymmetric LA remodeling [60].

Cardiac magnetic resonance imaging

CMR is recommended in case of inadequate echocardiographic windows and poor myocardial segment visualization (especially of the LV apex and anterolateral wall) for the establishment of HCM diagnosis [2, 22] (Fig. 5). CMR is an imaging technique with excellent spatial resolution and provides accurate measurements of maximal LV wall thickness (Fig. 6a) and detection of apical aneurysms, thrombi, and papillary muscle abnormalities [23, 61]. It has recently been indicated that myocardial crypts detected with CMR may represent a subtle feature of HCM in sarcomeric gene mutation-positive patients [24].

Late gadolinium enhancement (LGE) determines the presence and extent of myocardial fibrosis. LGE is present in about two thirds of HCM patients, typically in a patchy midwall distribution in areas of hypertrophy (Fig. 6b) or right ventricular insertion points [25] and is associated with regional wall motion abnormalities. The presence of LGE in HCM seems to be also associated with adverse outcomes, including cardiovascular mortality, heart failure death, and all-cause death [2, 62, 63].

Positron emission tomography

Chest pain and clinical signs of myocardial ischemia in the absence of epicardial coronary artery disease (CAD) are common in patients with HCM and in the majority of cases are due to small-vessel disease [64]. Positron emission tomography (PET) is a reliable noninvasive technique for the assessment of myocardial ischemia in the setting of microcirculatory dysfunction in HCM, the latter being associated with adverse prognosis [26, 65].

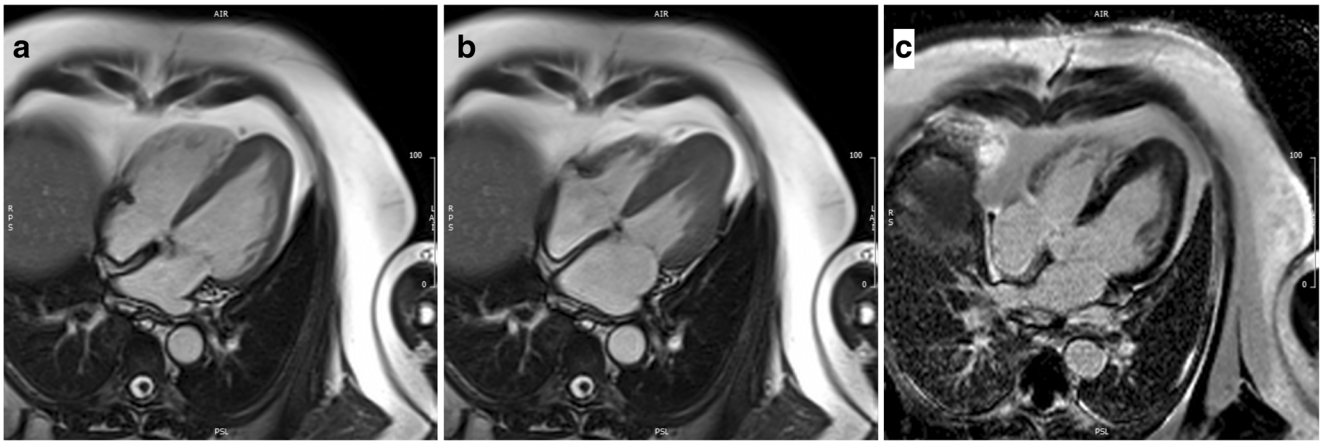

Fig. 5 CMR in apical HCM. **a** End-diastolic frame of the four-chamber cine showing the apical hypertrophy. **b** End-systolic frame of the four-chamber cine showing the obliteration of the cavity at the apex and the apical displacement of papillary muscles. **c** Late gadolinium enhancement image at the four-chamber view. Note the hazy enhancement of the apical segments due to myocardial fibrosis

Computed tomography

Assessment of epicardial coronary arteries is based on classical coronary angiography or CT coronary angiography. Apart from obstructive atherosclerotic lesions, myocardial bridges and intramuscular cardiac course of a vascular vessel resulting in compression during contraction can be revealed [27].

Exercise tests

Exercise tests are of low sensitivity for the detection of epicardial CAD due to coronary microcirculatory dysfunction; however, exercise echocardiography provides important information regarding the provocation of LVOT obstruction not present at rest, the response of blood pressure to exercise, and possible induction of ventricular arrhythmias [13].

Myocardial biopsy

Myocardial biopsy is used increasingly rarely as HCM diagnosis is based on clinical assessment. It is, however, recommended when there is a suspicion of infiltrative cardiomyopathy (i.e., amyloidosis) or storage diseases and the diagnosis cannot be made by other means [2].

Assessment of the risk of sudden cardiac death

Assessment of the risk of sudden cardiac death (SCD) is of paramount importance, since sudden death is considered the main cause of death in younger HCM patients. Conventional and nonconventional risk markers of SCD are summarized in Table 3.

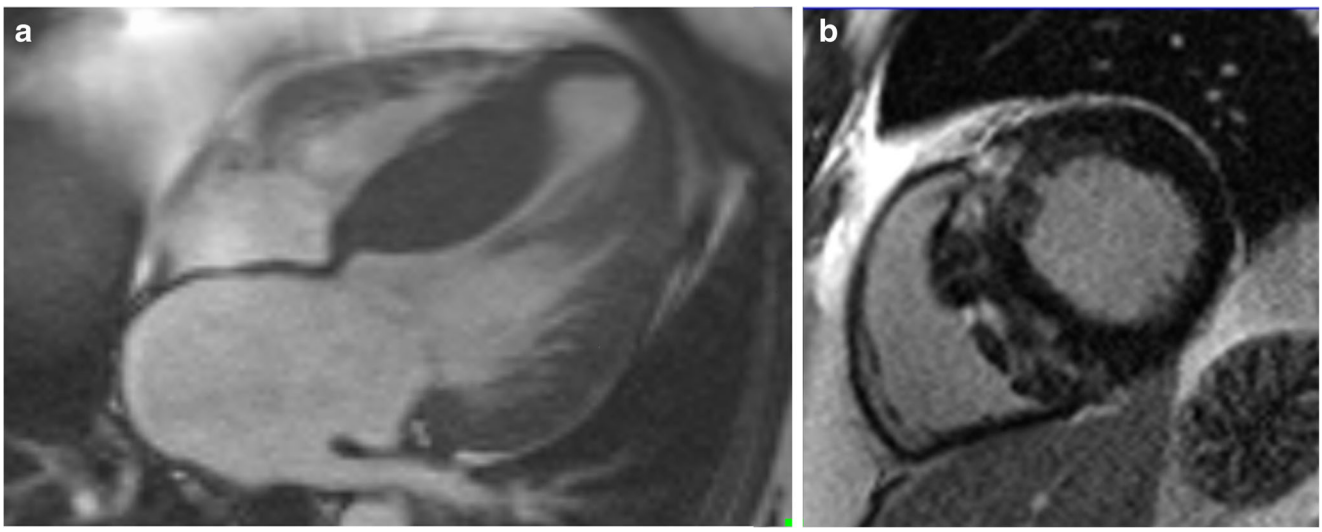

Fig. 6 Asymmetric hypertrophy of the interventricular septum by cardiac MRI. **a** End-diastolic frame of the four-chamber cine showing the interventricular septum hypertrophy. **b** Short-axis late gadolinium enhancement view showing a patchy midwall distribution of fibrosis in the hypertrophic interventricular septum

Table 3 Conventional and nonconventional risk markers of sudden cardiac death in hypertrophic cardiomyopathy (ref. [2, 20, 23, 59, 66–72)

Conventional risk markers	Nonconventional risk markers
History, demographic, and genetic risk markers	
• Age	• Multiple sarcomere protein gene mutations
• Family history of SCD in one or more first-degree relatives under the age of 40 or SCD in a first-degree relative with confirmed HCM at any age	
• History of unexplained syncope	
Electrocardiographic risk markers	
•Nonsustained ventricular tachycardia (3 consecutive beats at rate ≥ 120 b/min < 30 s duration on Holter monitoring	• Fragmented QRS complex
	• Heart rate variability in children with HCM
Imaging risk markers	
• Maximum LV wall thickness by transthoracic echocardiography	• Myocardial fibrosis ≥ 15% of LV mass by LGE on CMR
• Size of the LA by transthoracic echocardiography	• Large LV apex aneurysms with transmural and extensive myocardial scarring demonstrated by LGE and thrombus formation within the aneurysm
• Maximum LVOT gradient at rest or with provocation using pulsed and continuous wave Doppler	• GLS

LV left ventricular, *LVOT* left ventricular outflow tract, *GLS* global longitudinal strain, *LA* left atrium, *LGE* late gadolinium enhancement, *SCD* sudden cardiac death, *b/min* beats per minute, *CMR* cardiac magnetic resonance

Conventional risk markers of sudden cardiac death

A large amount of data indicate that risk stratification should be based on patient and family history, 48-h ambulatory ECG findings, and cardiac imaging (echocardiography or CMR) [2, 59].

The European Society of Cardiology (ESC) guidelines on HCM have introduced the use of a predictive score on the risk of SCD including:

(1) Age
(2) Maximum LV wall thickness by transthoracic echocardiography
(3) Size of the left atrium by transthoracic echocardiography (LA diameter in the parasternal long axis view with M-Mode or 2D)
(4) Maximum LVOT gradient at rest or with provocation using pulsed and continuous wave Doppler from apical five- and three-chamber views
(5) Family history of SCD in one or more first-degree relatives under the age of 40 or SCD in a first-degree relative with confirmed HCM at any age
(6) Nonsustained ventricular tachycardia (three consecutive beats at rate ≥ 120 b/min < 30 s duration on Holter monitoring)
(7) History of unexplained syncope

The formerly used abnormal blood pressure response to exercise has been lastly excluded as a risk factor. Patients at high risk for SCD (> 6% at 5 years) should be considered for ICD implantation, while a discussion on ICD implantation based on the particular risk factors is recommended for patients with lower SCD risk (4–6% at 5 years).

Nonconventional risk markers of sudden cardiac death

Another important issue is SCD prevention in HCM patients stratified in the "grey area" (of intermediate risk) for SCD, such as multiple sarcomere protein gene mutations being suggested as risk factors to guide ICD therapy in intermediate-risk patients [66], but there are few data to support this approach. Global longitudinal strain [20] and extent of myocardial fibrosis assessed with CMR have also been suggested as risk factors for SCD [67]. Myocardial fibrosis ≥ 15% of LV mass by LGE is associated with a twofold increase in SCD event risk with an estimated likelihood for SCD events of 6% at 5 years and reclassifies patients otherwise considered of low risk [67]. In HCM patients with low/intermediate ESC SCD risk score (2.3 ± 2.0 risk at 5 years) ≥ 15% of LV mass by LGE was associated with higher rates of the composite endpoint (SCD and appropriate ICD discharge). After 4.7 ± 2.0 years of follow-up, 4% of HCM patients met the composite endpoint and ≥ 15% LGE was associated with the composite endpoint similarly in obstructive and nonobstructive HCM patients (subhazard ratio 3.04, 95% confidence interval 1.48 to 6.10, $p = 0.003$ in obstructive; subhazard ratio 2.84, 95% confidence interval 1.27–6.34, $p = 0.01$ in nonobstructive HCM patients) providing incremental prognostic value over standard SCD risk stratification [68]. Therefore, patients may benefit from ICD implantation in the context of primary prevention. Patients with large LV apex aneurysms with transmural and often more extensive myocardial scarring demonstrated

by LGE and thrombus formation within the aneurysm have been indicated as high-risk patients for adverse cardiac events of 10.5%/year including SCD, appropriate ICD discharges, nonfatal thromboembolic stroke, and progressive heart failure and death [23]. On the contrary, LGE at right ventricular insertion points does not represent myocardial fibrosis and is not associated with high risk for adverse events and SCD [73].

Fragmented QRS complex (fQRS) on ECG may be a useful marker for prediction of ventricular arrhythmic events in patients with HCM. It has been indicated that during a mean follow-up of 6.3 years, fQRS strongly and independently predicted ventricular arrhythmic events defined as nonsustained or sustained ventricular tachycardia or SCD (adjusted hazard ratio 6.28, 95% confidence interval 2.49–15.84, $p < 0.001$) and major arrhythmic events defined as sustained ventricular tachycardia or SCD (adjusted hazard ratio 6.04, 95% confidence interval 1.49–24.39, $p = 0.011$) [69].

Moreover, fQRS seems to be associated with increased cardiovascular mortality in HCM (adjusted hazard ratio 2.68, 95% confidence interval 1.22–5.91, $p = 0.014$) [70].

Although HCM often presents with altered autonomic cardiac control [71], there is no solid evidence that analysis of heart rate variability in adults with HCM adds to the predictive accuracy for SCD over conventional risk stratification. However, it seems to have a prognostic value for SCD in children with HCM [72].

The electrophysiological study and programmed electrical stimulation are not recommended as prognostic tools for risk stratification. Electrophysiological study is recommended in supraventricular tachycardias and pre-excitation syndromes in order to identify and treat the ablatable substrates [2].

Genetic testing

Genetic testing is increasingly being applied to patients who meet diagnostic criteria for HCM in order to identify the causative mutation for the disease and to determine the genetic predisposition of asymptomatic relatives [2, 5]. Typically, HCM is inherited as an autosomal dominant genetic trait with a 50% risk of transmission to offspring, whereas sporadic cases of autosomal recessive inheritance are less common.

The patient is initially checked and once the responsible mutation is identified, genetic screening of first degree relatives is recommended [2]. In a case that the same mutation is identified in one or more relatives, initial clinical evaluation is recommended, followed by repeat assessment in long term basis at intervals depending on progression of the disease or the occurrence of cardiovascular symptoms (ECG + echocardiography). If the genetic test is negative for a definite HCM causing mutation the relatives are dismissed from future controls and reviewed only if they experience symptoms. Repeat clinical assessment is also indicated in relatives when genetic testing is not performed in the proband, or when there are more genetic variants of unknown importance (ECG + echocardiography at intervals depending on age of disease onset severity of the disease in the family) [33, 34]. Genotype positive phenotype negative individuals are considered of preclinical stage characterized by ECG, morphological and functional abnormalities [35, 74] with a rather benign course during this stage [11, 36].

Differential diagnosis

Particular attention is needed in the differential diagnosis from athlete's heart, hypertensive disease, cardiac amyloidosis, Anderson–Fabry disease, and isolated basal hypertrophy of the interventricular septum. Main criteria for the differential diagnosis are summarized in Table 2.

(a) The athlete's heart especially in the "overlap zone" between extreme expressions of athlete's heart and the mild HCM phenotype, of 13–15 mm [37, 38]. HCM is favored with LV end-diastolic cavity < 45 mm, abnormal LV filling pattern, identification of sarcomere mutation, T-wave inversion on ECG, and family history of HCM [39]. Additionally, LGE by CMR and absence of LV mass regression after short periods of deconditioning are features consistent with HCM diagnosis [40, 41]. Assessment of extracellular volume (ECV) by T1 mapping in CMR has also been applied in differentiation between HCM and athlete's heart. As LV hypertrophy increases in athlete's heart, there is a reduction in ECV, whereas increased ECV is associated with advanced "pathological" hypertrophy and increased myocardial disarray in HCM [42].

(b) Hypertension, where the ECG has no significant abnormalities or is characterized by the presence of LV hypertrophy with high voltage. Marked repolarization abnormalities and Q waves are unusual in hypertensive cardiomyopathy [43]. Maximum LV wall thickness < 15 mm (Caucasian) and < 20 mm (black) are findings consistent with hypertensive LV hypertrophy rather than HCM [44, 45]; however, an overlap zone of the degree of hypertrophy between these two conditions is not uncommon. Strict regulation of hypertension leads to regression of hypertrophy in hypertensive disease within a 6–12-month period. Severe diastolic dysfunction, family history of HCM, and extensive presence of LGE in CMR are features more consistent with HCM [2, 25].

(c) Anderson–Fabry disease, which is due to a deficiency of α-galactosidase and is characterized by LV hypertrophy, a variety of ECG abnormalities, and myocardial fibrosis. Enzyme replacement therapy may lead to regression of hypertrophy [47–49].

(d) Cardiac amyloidosis (CA) characterized by amyloid deposition in the cardiac tissue and manifested as restrictive cardiomyopathy in the early stages of the disease. Symptoms include dyspnea on exertion, abdominal distension, lower limb edema, orthostatic hypotension, and syncope. Low QRS voltage in ECG and increased ventricular wall thickness with granular sparkling appearance of the myocardium on echocardiography (Fig. 7, Fig. 8a) are characteristic findings of the disease [50, 51]. Other echocardiographic findings include thickening of cardiac valves and interatrial septum, diastolic dysfunction (Fig. 8b), reduced myocardial velocities in TDI (Fig. 8c), biatrial enlargement, and in advanced stages systolic dysfunction [52, 75].

However, none of these findings are specific for the diagnosis of cardiac amyloidosis. The significant decrease of longitudinal strain in the mid- and basal LV segments with relative preservation of the apical region has been found to be diagnostic findings with high sensitivity (93%) and specificity (82%) (area under the curve 0.94) in differentiating CA from others causes of LV hypertrophy including HCM (Fig. 8d) [76]. In the diagnosis of amyloidosis, the following also contribute: CMR–LGE pattern of distribution with diffuse subendocardial or transmural enhancement in combination with dark blood pool, as opposed to HCM in which LGE occurs in the midwall and shows patchy distribution [77], and 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy in the differential diagnosis between transthyretin-associated cardiac amyloidosis (TTR-amyloidosis) and HCM. In patients with TTR-amyloidosis, there is radio-drug uptake from the cardiac tissue in contrast to HCM that shows no radio-drug uptake [78, 79].

(e) Isolated hypertrophy (> 12–13 mm) of the basal segment of the interventricular septum with a proximal septum-to-mid/distal septum thickness ratio > 1.5 is often observed in the elderly, and differential diagnosis from genetic HCM may be challenging [53]. Absence of typical symptoms of HCM, absence of family history of HCM/SCD, absence of SAM and LVOT obstruction at rest, and septum thickness < 15 mm in combination with posterior wall thickness < 11 mm favor the diagnosis of isolated basal hypertrophy rather than HCM [54]. Furthermore, absence of a causative mutation at genetic testing and absence

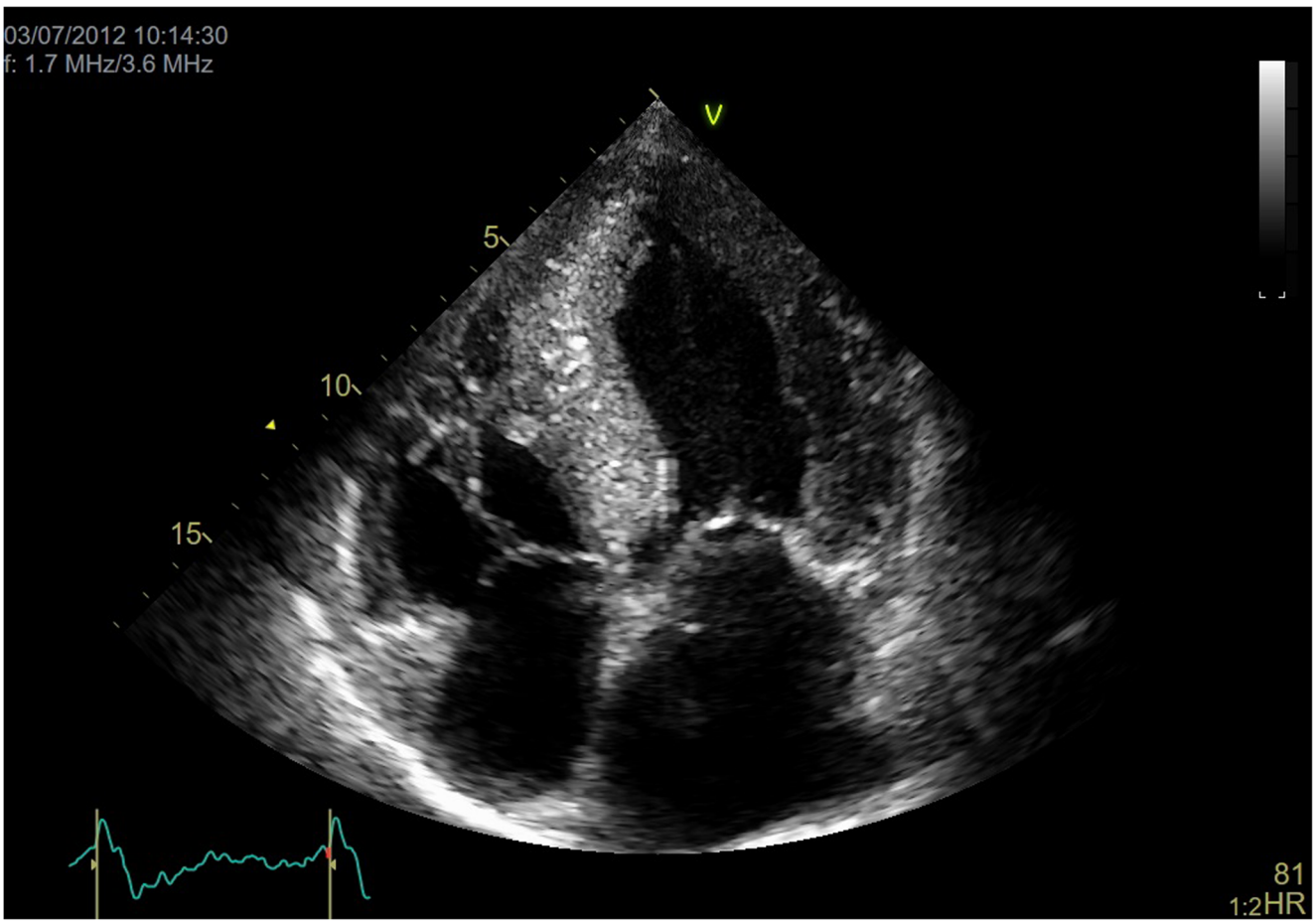

Fig. 7 Cardiac amyloidosis with increased thickness of the LV walls and sparkling appearance of the interventricular septum

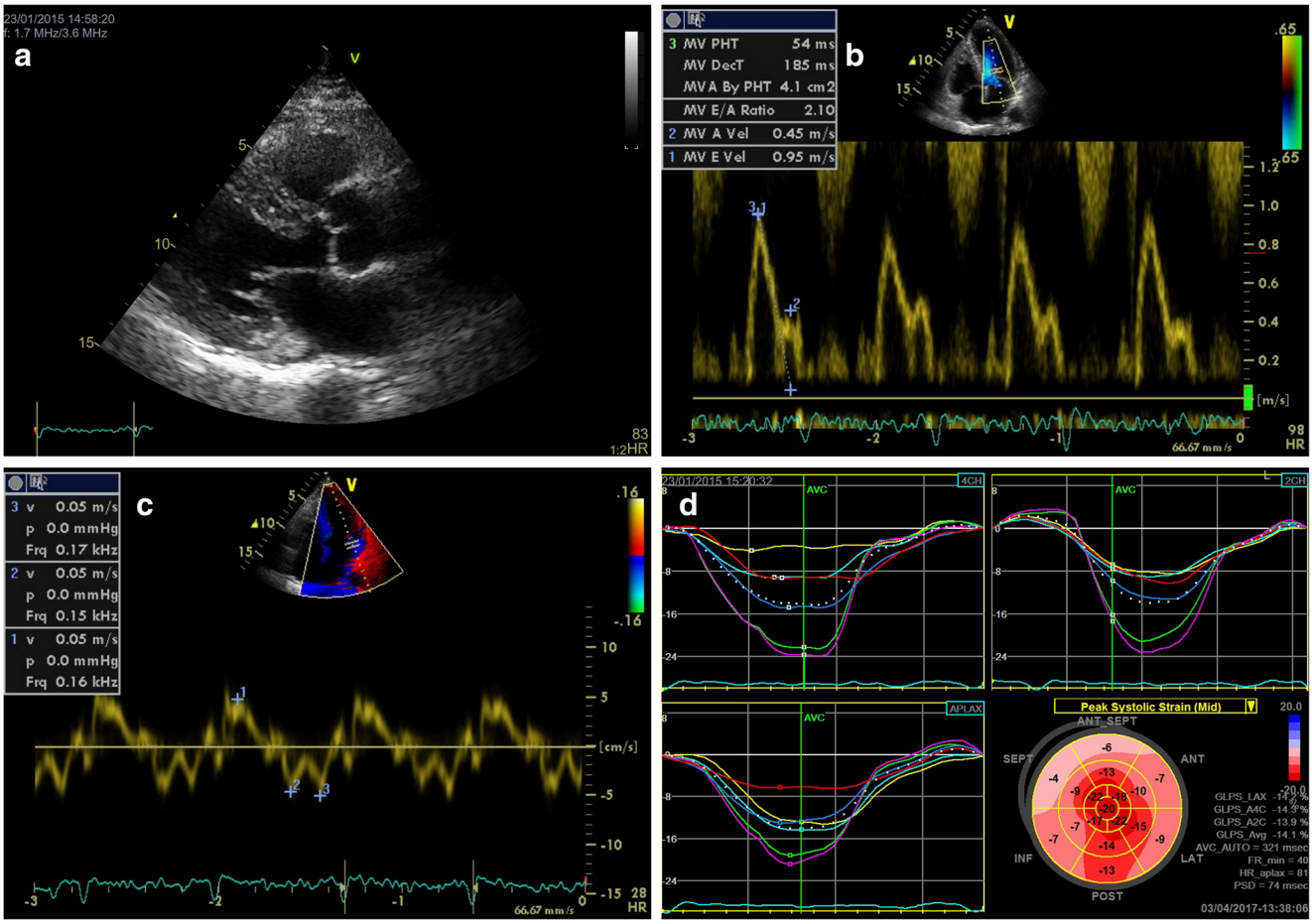

Fig. 8 Parasternal long-axis view with increased LV wall thickness in a patient with cardiac amyloidosis **a** with advanced diastolic dysfunction as indicated by a ratio *E*/*A* > 2 **b** and reduced myocardial velocites by tissue Doppler imaging. **c** Longitudinal strain has an "apical sparing pattern" with relatively preserved strain values of the apical segments and impaired strain values in the mid- and basal segments of the LV

of LGE by CMR may be supportive of isolated basal hypertrophy [54, 55].

Treatment

Management of hypertrophic obstructive cardiomyopathy

Pharmacological treatment of hypertrophic obstructive cardiomyopathy

Typical symptoms of HCM include dyspnea, chest pain, palpitations, and syncope. Treatment is aimed at improvement of symptoms, exercise capacity, and functional status, especially in patients with HOCM. First-line treatment includes β-blockers without vasodilatory effect (metoprolol, propranolol, atenolol, while nebivolol and carvedilol are contraindicated) [2, 80]. Patients with HOCM should avoid dehydration, arterial and venous vasodilators, and digoxin as all the aforementioned factors could increase intracavitary obstruction [81, 82]. Verapamil as monotherapy is recommended for improvement of symptoms in case of intolerance to β-blockers [2, 83]. However, verapamil should not be prescribed to HCM patients with reduced LVEF due to its known negative inotropism and should be used with caution in HOCM with high gradient and pulmonary hypertension [84].

If symptoms persist, it is recommended to add disopyramide in combination with either a β-blocker or verapamil [2, 85]. Diltiazem also has similar effects with verapamil [86].

If patients with LVOT obstruction develop pulmonary edema with hypotension, the use of inotropic drugs (doboutamine, dopamine) and vasodilators is contraindicated whereas intravenous administration of a β-blocker in combination with a vasoconstrictor (phenylephrine, nor-adrenaline) is recommended.

Invasive treatment of hypertrophic obstructive cardiomyopathy

Invasive treatment in HOCM is recommended when the maximum pressure gradient in the LV outflow exceeds 50 mmHg despite the maximum tolerated drug delivery and the patient

has moderate to severe symptoms (NYHA III or IV) or recurrent syncope [2].

Invasive techniques include surgical septal myectomy (Morrow procedure) [87] and alcohol septal ablation (ASA) by injection of alcohol into a septal perforator branch that supplies the hypertrophied segment of the basal septum [88, 89] after myocardial contrast administration in order to accurately determine the exclusive localization of the contrast to the basal septum [90, 91].

Both techniques aim at the reduction of septal mass, obstruction regression, and improvement of symptoms. Surgical myectomy is preferred when there are other surgical indications including mitral valve replacement or repair (in case of moderate to severe mitral valve regurgitation) or coronary bypass. A partial excision and realignment of ectopic, hypertrophic, or displaced papillary muscles can be incorporated in an extended myectomy. Myectomy can be also applied to patients with midcavity obstruction [92].

In general, myectomy is recommended in younger patients while ASA in older HCM patients with substantial co-morbidities, which cause a higher surgical risk.

Despite similar efficacy of septal myectomy and ASA in terms of gradient reduction, improvement of symptoms, and improvement of long-term survival similar to the general population levels [93], there is no direct comparison between these two techniques in a randomized clinical trial. However, data from several meta-analyses indicate improvement of functional status with a similar procedural mortality. In Liebregts's post-analysis, long-term mortality (mean follow-up 6.2 years) was similarly low between septal myectomy and ASA (septal myectomy 1.4% per year vs 1.5% per year for alcohol ablation, $p = 0.78$). ASA is associated with a substantial risk for atrioventricular block, requiring permanent pacemaker implantation. A permanent pacemaker was implanted in 10% of patients with ASA and 4.5% in myectomy ($p < 0.001$). Moreover, a repetitive intervention was more often required in ASA 7.7% vs 1.6% in myectomy $p = 0.001$ [94].

In Vriesendorp's post-analysis in a 10-year follow-up, survival in patients with myectomy was 85% similar to that of ASA at 82%. However, multivariate analysis showed that ASA was an independent factor for sudden death compared to myectomy (HR 2.1, $p = 0.04$). Patients treated with ablation activated ICD more often (20%) than patients treated with myectomy (3.5%) [95]. Apart from the fact that these observations were partially based on data from the only study that showed excess mortality after ASA [96] and has been criticized in terms of the technique used [97, 98], survival free of SCD after ASA has been shown to be very high in numerous studies of medium- to long-term follow-up. Additionally, the risk factors for SCD appear to diminish significantly after ASA [91, 99].

In the Euro ASA registry with 1275 patients who had ASA, the 30-day mortality was 1%, and the 10-year survival was 77%, respectively. In multivariate analysis, independent prognostic indicators for mortality after ASA were age, septal thickness before ASA, NYHA class, and LVOT pressure gradient after ASA [99]. For every 1-mmHg increase in the residual pressure gradient, long-term mortality increased by 1%. Therefore, in ASA, it is very important to aim for the significant reduction in septal thickness in order to minimize the risk for residual obstruction.

Moreover, the appropriate choice of patients is also a crucial parameter as it has recently been indicated that younger (< 50 years) patients treated with ASA had better outcomes compared to older patients in terms of 30-day and long-term survival and pacemaker implantation rates. Thus, ASA could be expanded to younger patients with good results [100].

Alternative methods of septal ablation have been recently introduced. Endocardial radiofrequency (RF) ablation can be applied directly from the LV endocardial surface by bypassing the access from coronary arteries and can result in modest reduction of basal septal hypertrophy LVOT gradients and functional class [101, 102].

Treatment of heart failure in hypertrophic cardiomyopathy

Patients with HCM with symptoms of HF and impaired LVEF < 50% without LVOT obstruction should be treated with ACE/ARBs, β-blockers, low-dose loop diuretics, and mineralocorticoid receptor antagonists [2].

Heart transplantation should be considered in symptomatic patients with LVEF < 50% and NYHA III–IV despite optimal medical therapy, whereas symptomatic patients with LVEF > 50%, NYHA III–IV, and severe diastolic dysfunction despite medical therapy may be also considered for transplantation [2].

The survival of HCM patients undergoing heart transplantation is similar to that for non-HCM causes and superior to that for CAD with acute rejection being relatively rare [103, 104].

Management of atrial fibrillation in hypertrophic cardiomyopathy

Atrial fibrillation (AF) is the most common arrhythmia in patients with HCM. Prevalence and annual incidence of AF is 22.5% and 3.1%, respectively, whereas prevalence and annual incidence of thromboembolism in HCM patients with AF is 27.1% and 3.8%, respectively [105]. Heart failure and thromboembolism are the main complications and the leading causes of death in elderly patients with AF and HCM [106]. Left atrial remodeling due to elevated LV filling pressures, mitral regurgitation, LVOT obstruction, and age are the main factors responsible for AF [2]. It is recommended that HCM patients in sinus rhythm with LA diameter ≥ 45 mm should

undergo 48-h ambulatory ECG monitoring to detect AF every 6–12 months [2].

In case of new-onset AF with hemodynamic instability, direct current cardioversion is recommended whereas in hemodynamically stable patients, i.v. amiodarone should be used for restoration of sinus rhythm and for achieving rhythm control. β-Blockers, verapamil, and diltiazem are recommended for slowing rapid ventricular response in hemodynamically stable patients, whereas digoxin should be avoided in case of LVOT obstruction [2]. Class IC antiarrhythmics, such as flecainide and propafenone, should be avoided due to the risk of prolongation of the QRS duration and the QT interval, that may result to conversion AF to atrial flutter with increased 1:1 ventricular conduction [2]. Regarding prevention of thromboembolism in HCM, use of the CHA2DS2-VASc score to calculate stroke risk is not recommended. It is recommended that HCM patients with AF should receive lifelong treatment with vitamin K antagonists (VKAs) with a target international normalized ratio between 2.0 and 3.0, even after restoration of sinus rhythm [2]. There are no solid data on the use of new oral anticoagulants (NOACs) (e.g., apixaban and rivaroxaban [factor Xa inhibitors], or dabigatran [thrombin inhibitor]), in patients with HCM, but they are recommended in case of failure of maintenance or failure of monitoring therapy with VKAs. Ventricular rate control using β-blockers and nondihydropyridine calcium channel antagonists (verapamil, diltiazem) is recommended in patients with paroxysmal, persistent, or permanent AF [2].

Catheter ablation for AF should be considered in patients without severe LA enlargement, who have drug-refractory symptoms or are unable to take anti-arrhythmic drugs [107]. Catheter ablation is a safe and effective procedure for patients with HCM [107, 108]; however, usually more ablation procedures are required to achieve sinus rhythm compared with patients without HCM [109]. In a recent meta-analysis of 15 studies, freedom from atrial arrhythmia after a single procedure was 45% [110]. After multiple ablation procedures, the overall success rate was 66%. The final success rate was 72% in patients with paroxysmal AF and 47% in persistent AF. Even after successful ablation, antiarrhythmic therapy was often required to maintain sinus rhythm. Without anti-arrhythmic drugs, the success rate even after multiple procedures was 50.4% [110].

Pregnancy and hypertrophic cardiomyopathy

Women with HCM usually tolerate pregnancy well. Recently, a meta-analysis indicated maternal mortality of 0.5%, and worsening of symptoms related to HCM in 29% of cases [111]. The risk of premature birth was increased (26%) [111]. Risk of death and cardiovascular complications is increased in HCM women in case they are symptomatic pre-pregnancy or exhibit a high-risk profile including diastolic dysfunction, severe LVOT obstruction, and arrhythmias [2, 112].

Adequate and timely counseling on contraception, the risks associated with pregnancy, and the risk of disease transmission to the child is important in HCM women [2]. According to World Health Organization (WHO) classification [2], most HCM patients are WHO class II (mild to moderate LVOT obstruction, asymptomatic with or without medication, well-controlled arrhythmia, normal systolic LV function, or mild LV dysfunction) or WHO class III (severe LVOT obstruction, symptoms or arrhythmias despite optimal medication, moderate systolic LV dysfunction). Pregnancy is contraindicated in WHO class IV with severe symptomatic LVOT obstruction or severe systolic LV dysfunction [2]. Women in WHO class II should be assessed each trimester, and those in WHO class III should be assessed monthly or bimonthly [112]. Symptomatic status, LVOT obstruction, arrhythmias, and ventricular function should be assessed. Echocardiography should be performed each trimester or when new symptoms occur.

Beta-blockers should be continued if they are already being taken. They should be started when new symptoms occur (preferably metoprolol), for rate control in AF, and for ventricular arrhythmia suppression (with monitoring of fetal growth or for occurrence of fetal atrioventricular block) [2]. Verapamil can be administered when beta-blockers are not tolerated [2]. Cardioversion is safe and should be considered for poorly tolerated AF. Anticoagulation is recommended for those with paroxysmal or persistent AF. Low molecular weight heparin with anti-factor-Xa monitoring (peak anti-Xa level 0.8–1.2 U/mL 4–6 h post-dose) in the first trimester and from the 36th week onwards, or VKAs in the second and third trimester are recommended for paroxysmal or persistent AF [112]. NOACs are not recommended because of proven toxicity in animals and insufficient data in humans. When indicated, pacemaker or ICD implantation during pregnancy should be performed, preferably with echocardiographic guidance [112, 113].

Competitive sports in hypertrophic cardiomyopathy

Participation in high-intensity competitive sports itself may induce life-threatening ventricular arrhythmias and acts as a potent independent risk factor for SCD in HCM patients, even in the absence of the conventional risk markers [114].

According to current guidelines, restriction from competitive sports is recommended in patients with HCM [2]. Conversely, retrospective data indicate that SCD is relatively rare among HCM patients who exercise regularly [115]. It has recently been indicated that in a small cohort of 35 athletes with HCM during a 9-year follow-up period, there were no differences in the incidence of symptoms or major events between athletes who had become sedentary after diagnosis and athletes who continued participating in competing sports [116]. Current data indicate that not all HCM patients participating in

exercise programs are at increased risk for fatal arrhythmias. Thus, engagement in competing sports may be reasonable after fully considering disease characteristics, the age of the athlete, duration in competitive sports prior to HCM diagnosis, and the presence of conventional risk factors for SCD.

According to recent ESC recommendations for participation in competitive and leisure time sports in athletes with cardiomyopathies [117], conditions that reasonably represent absolute contraindications for competitive sports participation include:

(1) History of aborted SCD/cardiac arrest
(2) Symptoms, particularly unheralded syncope
(3) Exercise-induced ventricular tachycardia
(4) High ESC 5-year risk score
(5) Significant increase in LV outflow gradient (> 50 mmHg)
(6) Abnormal blood pressure response to exercise

On the contrary, adult athletes with mild clinical expressions of HCM and low ESC risk score may be selectively allowed to participate in all competitive sports, with the exception of those where syncope may be associated with harm or death.

Novel therapies currently being applied in HCM

There are completed and ongoing clinical trials investigating the effectiveness of novel pharmacological treatment in HCM, mainly for the prevention or regression of LV hypertrophy in early stages of the disease. Clinical trials of novel pharmacological therapies are summarized in Table 4. In the INHERIT trail, 133 patients with HCM were randomized to receive either 100 mg of losartan or placebo. The primary endpoint was the reduction of the LV mass, whereas secondary endpoints included changes in the amount of LV fibrosis as assessed by LGE on MRI, maximum LV wall thickness, LA volume, and plasma levels of NT-pro-brain natriuretic peptide. After 12 months, no reduction in LV mass was observed in the losartan arm, and there was no difference in LV mass change with the placebo arm. The same was true for all secondary endpoints [118].

The VANISH trial is an ongoing randomized trial, testing the modification of the disease with valsartan in sarcomere mutation carriers with HCM and no/minimal symptoms, or those with early phenotypic manifestations but no LV hypertrophy [119].

Diltiazem has been tested as a disease modifier in sarcomere mutation carriers, and it has been indicated that diltiazem may improve LV remodeling in HCM [120].

In the RESTYLE-HCM trial, the effects of the late sodium current inhibitor ranolazine were tested on functional capacity using cardiopulmonary exercise test, symptomatic status, diastolic function, and arrhythmias in nonobstructive HCM patients. Patients were randomly assigned to placebo or ranolazine for 5 months. Ranolazine showed no overall effect on exercise performance, natriuretic peptide levels, diastolic function, or quality of life. However, ranolazine was associated with reduced premature ventricular complex burden (> 50% reduction vs baseline in 61% with ranolazine vs 31% for placebo; $p = 0.042$) [121].

As with ranolazine, eleclazine, a novel late sodium current inhibitor, showed no efficacy on exercise capacity in HCM, which resulted in premature termination of the LIBERTY-HCM trial [122].

Mavacampten is a novel, oral, allosteric modulator of cardiac myosin being developed for the treatment of HCM aiming to reduce cardiac muscle contractility by inhibiting the excessive myosin-actin crossbridge formation that underlies the excessive contractility. In the ongoing EXPLORER-HCM trial, administration of mavacamten is being tested in terms of reduction in LVOT obstruction, improvement in symptom severity as assessed by NYHA class, and increase in exercise capacity assessed by measurement of peak oxygen consumption by cardiopulmonary exercise testing in symptomatic obstructive HCM [123].

Spironolactone is being tested for relief and/or regression of the fibrotic process in HCM in an ongoing trial [124].

Perhexiline, is a metabolic modulator that inhibits the metabolism of free fatty acids and enhances carbohydrate utilization by cardiomyocytes towards an improvement of energy homeostasis in HCM. It was initially indicated that perhexiline improved the ratio of myocardial phosphocreatine to adenosine triphosphate in the myocardium, resulting in improved diastolic function and exercise capacity [125]. However, lack of efficacy of perhexiline in terms of outcomes and exercise capacity in HCM with moderate to severe heart failure resulted in premature termination of a clinical study designed to enroll 320 HCM patients [126].

Gene therapy seems a promising treatment option in HCM caused by mutations in genes encoding sarcomeric proteins. MYBPC3 trans-splicing and gene replacement in human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) has been tested in HCM with heterozygous mutation in the MYBPC3 gene aiming towards regression of hypertrophy and partial restoration of normal gene expression [127].

Moreover, recent advances in genome modification technologies, such as clustered regularly interspaced short palindromic repeats (CRISPR/cas9) system, facilitating specific editing of individual gene mutations may lead to individual-based pharmacological approaches in HCM [128].

Prognosis

With the contemporary treatments for HCM, mortality due to the disease is low, and HCM patients have normal or near-normal life expectancy without significant adverse events. However, given the clinical and genetic heterogeneity of the disease, a number of HCM patients are at risk for adverse

Table 4 Ongoing and completed randomized clinical trials assessing novel pharmacological therapy in patients with hypertrophic cardiomyopathy (ref. [118–128])

Name of the study or first author	Drug	Number of patients	Endpoint	Results	Year of publication
Abozguia et al.	Perhexiline 100 mg vs placebo	46 patients with nonobstructive symptomatic HCM	Efficacy on diastolic function and exercise capacity	Improvement of diastolic function and increased peak oxygen uptake	2010
INHERIT trial	Losartan 100 mg vs placebo	124 patients with obstructive or nonobstructive HCM	Effects on LVH and fibrosis	No reduction in LVH	2015
Ho et al.	Diltiazem 360 mg/die vs. placebo	38 sarcomere mutation carriers without LVH	Safety, feasibility, and effect of diltiazem as disease-modifying therapy	Improvement in early LV remodeling in HCM	2015
VANISH trial	Valsartan up to 160 mg vs. placebo	211 sarcomere mutation carriers with HCM and no/minimal symptoms NYHA class I–II, or those with early phenotypic manifestations but no LV hypertrophy	Attenuating disease evolution in early sarcomeric hypertrophic cardiomyopathy	Ongoing PHASE II NCT01912534	
RESTYLE-HCM	Ranolazine 1000 mg bid vs placebo	80 nonobstructive HCM patients	Functional capacity using cardiopulmonary exercise, symptomatic status, diastolic function, and arrhythmias in nonobstructive	No overall effect on functional capacity, diastolic function, quality of life Reduced premature ventricular complex burden	2018
EXPLORER-HCM	Mavacamten vs placebo	220 patients with symptomatic obstructive hypertrophic cardiomyopathy	Reduction in LVOT obstruction, improvement in symptom severity from baseline to week 30 as assessed by NYHA functional classification (e.g., I, II, III, or IV), and increase in exercise capacity from baseline to week 30 as assessed by measurement of peak oxygen consumption determined by cardiopulmonary exercise testing	Ongoing Phase III NCT03470545	
Maverick-HCM	Mavacamten vs placebo	60 adults with symptomatic nonobstructive hypertrophic cardiomyopathy	Frequency and severity of treatment-emergent adverse events and serious adverse events	Ongoing PHASE II NCT03442764	
Evaluating the Effect of Spironolactone on Hypertrophic Cardiomyopathy	Spironolactone vs not taking spironolactone	260 HCM patients	LV fibrosis by LGE	Ongoing Phase 4 NCT02948998	
LIBERTY-HCM	Eleclazine (GS-6615)	172 patients with symptomatic HCM	Exercise capacity as measured by peak oxygen uptake achieved during cardiopulmonary exercise testing	Lack of efficacy (terminated) Phase II/III NCT02291237	
–	Perhexiline 100 mg (sponsor: Heart Metabolics Ltd) vs. placebo	320 patients with HCM and moderate to severe HF	Hierarchical classification of outcome variable and change in maximum oxygen consumption after 6 months	Lack of efficacy (withdrawn) Phase III NCT02431221	

LV left ventricular, *LVH* left ventricular hypertrophy, *NYHA* New York Heart Association

outcomes related to HCM, including heart failure and SCD. In a recent meta-analysis of 19 studies including 12.146 HCM patients, the pooled 1-, 3-, 5-, and 10-year survival rates were 98.0%, 94.3%, 82.2%, and 75.0%, respectively. Age, NYHA class, family history of sudden death, syncope, AF, nonsustained ventricular tachycardia, maximum LV wall thickness, and LV obstruction were significant prognostic factors for cardiovascular death. Estimation of population attributable risk indicated that nonsustained ventricular tachycardia was the strongest predictor for cardiovascular death (13.02%, 95% confidence interval 3.60–25.91%), while LVOT obstruction/midventricular obstruction was the strongest predictor for all-cause death and SCD (10.09%, 95% confidence interval 4.72–20.42% and 16.44%, 95% confidence interval 7.45–31.55%, respectively). Thus, early identification of prognostic factors is crucial in order to permit timely interventions to reduce cardiovascular complications and improve survival rates of HCM patients [129].

Conclusions

In conclusion, the correct diagnosis of hypertrophic cardiomyopathy requires the correct application of echocardiography in combination with advanced imaging techniques such as CMR. Genetic testing is an integral part of clinical practice as it carries both diagnostic and prognostic value. The MOGE(s) approach enables a standardized classification of cardiomyopathies, including HCM. Furthermore, the ESC predictive model for SCD has a central role for the appropriate risk stratification and primary prevention. Differential diagnosis between HCM and other diseases with LV hypertrophy has significant impact on prognosis and treatment strategies. Treatment is based on pharmacological therapy, surgery, and invasive treatment with alcohol septal ablation aiming at the reduction of symptoms and improvement of functional capacity.

Compliance with ethical standards

Disclosures Michel Noutsias has received grants from the Deutsche Forschungsgemeinschaft (DFG) through the Sonderforschungsbereich Transregio 19 "Inflammatory Cardiomyopathy" (SFB TR19) (TP B2) and from the University Hospital Giessen and Marburg Foundation Grant "T cell functionality" (UKGM 10/2009). Michel Noutsias has been consultant to the IKDT (Institute for Cardiac Diagnosis and Therapy GmbH, Berlin) in 2004–2008, and has received honoraria for presentations and/or participated in advisory boards from Abiomed, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Fresenius, Miltenyi Biotech, Novartis, Pfizer, and Zoll.

Conflict of interest The authors declare that they have no conflicts of interest.

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The manuscript does not contain clinical studies or patient data.