Figure 7. Flow chart for the management of suspected HCM. 24-h ABPM, 24-hour ambulatory blood pressure monitoring; CMR, cardiac magnetic resonance; CT, computed tomography; DPD, diphosphonates; ECG, electrocardiogram; ESRD, end-stage renal disease; HCM, hypertrophic cardiomyopathy; HFpEF, heart failure with preserved ejection fraction; HT, hypertension; MRI, magnetic resonance imaging.

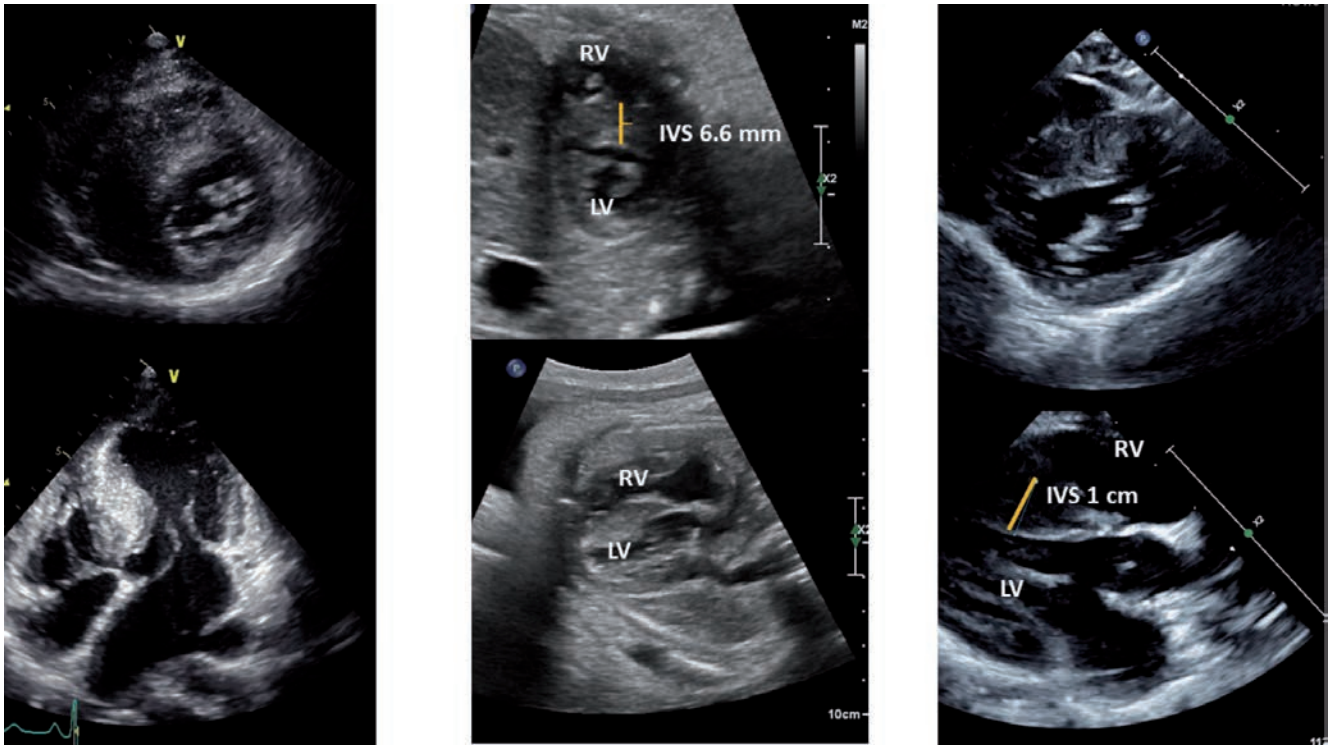

Figure 8. Mother and child with hypertrophic cardiomyopathy. A) Mother with S/P myomectomy in left ventricular outflow tract obstruction; first pregnancy ended with spontaneous abortion; genetic testing result of the fetus was Turner syndrome; second pregnancy: prenatal diagnosis of hypertrophic cardiomyopathy of the fetus. B) Fetus: moderate to severe hypertrophic myocardium mainly in the interventricular septum (IVS); echo at 34 weeks. C) Baby boy with hypertrophic cardiomyopathy at 5 months; gene expression of TPTN11 variant (Leopard); counseling could have helped planning the second pregnancy. LV, left ventricle; RV, right ventricle.

nel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and high-dose diuretics.

Mavacamten is a first-in-class cardiac myosin inhibitor indicated in symptomatic obstructive hypertrophic cardiomyopathy with LVOT gradient ³50 mmHg. Mavacamten is an allosteric modulator of cardiac myosin and acts reducing cardiac muscle contractility by inhibiting excessive myosin-actin cross bridge formation. The EXPLORER-HCM phase 3 trial, showed a reduction in LVOT gradient after exercise (-36 mmHg), greater increase in pVO2 (+ 1.4 ml/Kg/min), improved symptoms score, NYHA functional class, and the overall quality of life [99].

Patients with LVOT, who remain unresponsive to medical therapy can opt for septal reduction therapy in the form of surgical ventricular septal myectomy (Morrow procedure) or alcohol septal ablation, particularly among patients with NYHA functional class III or class IV. Transaortic extended septal myectomy is appropriate covering a broad range of patients with symptomatic, obstructive HCM [100,101].

The most effective strategy for lengthening life and preventing fatal, life threatening tachyarrhythmias is an implantable cardioverter-defibrillator (ICD), especially in high risk population [102]. This therapy proved to be equally as beneficial in children and adolescent with extreme left ventricular hypertrophy being the most common risk factor associated with future ICD interventions [103]. Adult and pediatric that have progressive left ventricular diastolic or systolic dysfunction that is refractory to pharmacological therapy may be candidates for cardiac transplantation or mechanical circulatory support [104]. All patients are also advised to stop excessive alcohol consumption, avoid dehydration, and are motivated to lose weight (Table 4) [7,99,105-125].

Prognosis

The majority of individuals with HCM are able to enjoy an active lifestyle and tend to live the average lifespan. This is particularly true for patients with HCM without significant LVOTO, however special considerations must be discussed thoroughly with patients regarding pregnancy, and physical exercise [7]. The most common HCM related death is due to sudden cardiac death (SCD), but with the evolution of contemporary medicine and treatment modalities, the overall mortality can effectively be reduced to <1% per year [126]. In Table 5 subtypes of HCM are reported [127-145].

Sudden death

Sudden cardiac death is an unpredictable and devastating complication of HCM [146]. The pathophysiology is complex and not completely understood but genetic and molecular substrate, myofibrillar disarray, ventricular hypertrophy, microvascular

Table 4. Treatment options for patients with hypertrophic cardiomyopathy.

Pharmacological drug	Uses	Adverse events
Beta-blockers (non-vasodilating)	Abolish and reduce resting provocable LVOTO; Provide symptomatic relief; Suppress arrhythmia [105-107]	Hypotension [7]
Disopyramide (Class IA anti-arrhythmic)	Abolish basal LV outflow pressure gradients; Improves exercise tolerance [108,109]	Dry eyes and mouth, urinary hesitancy or retention, and constipation; Prolonged QT [109]
Verapamil or diltiazem (non-dihydropyridine)	Increase exercise capacity; Improve symptoms; Normalize or improve LV diastolic filling [110-113]	Pulmonary edema in patients with elevated pulmonary artery systolic pressure [114]
Low dose loop or thiazide diuretics	Improve dyspnea associated with LVOTO [7]	Hypovolemia worsening LVOTO [7]
Mavacamten	Improves exercise capacity and LVOTO; Improves overall quality of life [99]	Atrial fibrillation and decreased LV ejection fraction at high concentrations [99]
Invasive therapy	**Uses**	**Adverse events**
Ventricular septal myectomy	Reduces LVOT gradient; Reduces systolic anterior motion MR; Improves exercise intolerance [115,116]	AV nodal block; Ventricular septal defect; Aortic regurgitation [117]
Septal alcohol ablation	Reduces LVOT gradient; Symptom improvement; Increased exercise tolerance; Larger residual LV outflow tract gradients [118]	AV block [119]
Dual chamber pacing	Reduces LVOT gradient; Improves symptoms and quality of life [120,121]	Spontaneous backup reversion, unexpected battery depletion, total loss of telemetry without change in pacing mode [122]
Mitral clip	Used to target SAM causing dynamic LVOTO; Improves symptoms and quality of life	Recurrency of MR [123,124]
Cardiac transplant	Improves survival; Only treatment option for drug refractory cases without LVOTO [125]	Rejection, cardiac allograft vasculopathy, immunosuppressants effects

AV, atrio-ventricular; LV, left ventricular; LVOT, left ventricular outflow tract; LVOTO, left ventricular outflow tract obstruction; MR, mitral regurgitation; SAM, systolic anterior motion.

ischemia and fibrosis predispose patients with HCM to re-entrant ventricular arrhythmias [147,148]. While it seems that there is no difference in SCD based on gender, age is an important factor. Patients younger than 35 years of age are particularly affected although 20% of SCD occurs in patients older than 65 years [149,150]. The European Society of Cardiology developed a risk-SCD calculator where are included age, maximum LV wall thickness, left atrium, max LVOT gradient, family history of SCD, non-sustained VT, unexplained syncope (AHA HCM SCD calculator) [7].

To avoid this tragic event and in other patients is important to have the correct diagnosis. For this reason a complete autopsy must be performed according to well defined protocols; in case of death a molecular "autopsy" can diagnose the cause of death in 35% of patients [151]. In Saudi Arabia it is rarely performed but tissue samples from patients who underwent myomectomy and heart transplantation should be collected and preserved also for future pathologically revised using different techniques.

Long term outcome

The clinical course of HCM is less favorable in patients with the obstructive form of the disease and in the young compared to adult patients. Moreover, a small subgroup may progress to LV systolic dysfunction (ejection fraction less than 50%), wall thinning, apical aneurysm, chamber enlargement, and progressive symptoms of heart failure. These patients are also at high risk of sudden death [19,132,133,142,144]. Surgical relief of LVOT obstruction, ICD implantation and medical therapy changed the natural history of the disease, nevertheless heart failure and AF, especially in patients diagnosed at younger age and with sarcomere mutations, are still determinant factors of morbidity and mortality [117-120,125]. Heart failure is the clinical picture of the advanced stage of the disease, congestive heart failure therapy is recommended and later on heart transplantation can be the only definitive option to extend HCM patient life [152,153] (Table 6).

Table 5. Different phenotypes of hypertrophic cardiomyopathy and correlated prognosis.

Subtype	Percentage of subtype	Prognosis	Age of development	Genetics	Complications
Isolated basal septal hypertrophy [128-130]	46%	15-year survival similar to the general population	Elderly	Less than 10% of those having positive findings with the same genetic test	Angina and dizziness. Hypertension and coronary artery disease. Systolic anterior motion
Reverse septal curvature [128,131]	40%	Unfavorable prognosis with increased septal thickness at end diastole/left ventricular end-diastolic diameter ratio	Young population	Genetic test for myofilament HCM (in 80%), MYH7	Often associated with a family history of SCD, hypertension, and increased LVOT pressure, syncope
Apical HCM [132-134]	25% in Japan to 2% in western countries	Good	Middle aged men	Most common mutations: MYBPC3 and MYH7	Rarely associated with SCD, associated with hypertension
Mid-cavity hypertrophy (midventricular). Could be complicated by apical aneurysm [135-138]	2-5%	Midventricular obstruction is strongly associated with adverse effects	Middle aged men	44% of patients with midventricular obstruction was associated with some form of cardiomyopathy associated genetic variant. 21% had a mutation in sarcomere protein (5.9% MYH7, 12% MYBC3)	Higher incidence of clinical events. Risk of SCD of 5% per year, ventricular arrhythmia, myocardial necrosis, systemic embolism, obstruction and increased gradient at midventricular level
Symmetrical HCM [138,139]	42%	Variable	Middle aged		LVOTO is common
Asymmetric (septal) HCM [140-142]	60-70%	Good	Middle aged men		Resting systolic pressure gradient of the LVOT caused by SAM of the mitral valve leaflets, mitral regurgitation
Mass-like HCM [138,143]	Rare				DD with neoplastic masses Diagnosis by MRI LVOTO seen if thickening is at basal region
Non-contiguous HCM [144,145]	Found in 42 (13%) of 333 patients		35-73		Dyspnea, sleep apnea

DD, differential diagnosis; HCM, hypertrophic cardiomyopathy; LVOT, left ventricular outflow tract; LVOTO, left ventricular outflow tract obstruction; MRI, magnetic resonance imaging; SAM, systolic anterior motion; SCD, sudden cardiac death.

Table 6. Therapy in associated condition that complicate hypertrophic cardiomyopathy.

Clinical conditions associated with HCM		
Dyspnea and angina in non-LVOTO	Beta-blockers (propranolol, atenolol, nadolol, metoprolol, bisoprolol)	Bisoprolol in end-stage HF and usually not useful in LVOT
	Oral diuretics	Despite the use of beta-blockers or calcium channel blockers
	ACEi or ARB	(EF <50%)
	MRA	(EF <50%)
AFVentricular rate control	Bisoprolol or carvedilol	LV systolic dysfunction
	Verapamil or diltiazem	Only with preserved LVEF
	Digoxin	Only if LVEF <50% and no LVOTO
Prevention of cardioembolic events	NOAC	Independently of CHA2DS2-VASc score
Prevention of AF recurrences	Amiodarone, sotalol (Class III antiarrhythmic drug)	
	Disopyramide	In LVOTO associated with beta-blockers and verapamil
HF	ACEi or ARB	HF with reduced EF
	Sacubitril/valsartan	
Ventricular arrhythmias		
Reduction of NSVT	Amiodarone	
	Sotalol	
Reduction of symptomatic tachycardia	Amiodarone	
or recurrent shock (ICD)	Beta-blockers	

ACEi, angiotensin-converting enzyme inhibitor; ARBs, angiotensin receptor blocker; CHA2DS2-VASc, Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65-74 years, Sex category (female); EF, ejection fraction; HF, heart failure; ICD, implantable cardioverter-defibrillator; LV, left ventricular; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; LVOTO, left ventricular outflow tract obstruction; MRA, mineralocorticoid receptor antagonist; NOAC, new oral anticoagulant; NSVT, non-sustained ventricular tachycardia.

Telemedicine and teleconsulting

The experience of the SHaRe registry has shed new light on the importance of telemedicine and teleconsulting for the diagnosis and management of HCM, allowing a better understanding of the factors contributing to the heterogeneous outcomes in this complex disease [154,155]. The European Reference Network for Rare and Low prevalence Complex Diseases of the Heart (ERN-GUARD Heart) has been conceived as a virtual network involving healthcare providers across Europe aiming to give patients affected by rare and complex heart disease access to highly-specialized centers and best standards of care [96]. In addition, the spread of COVID-19 pandemic and the restrictions imposed by local Governments significantly limited patients and healthcare professionals' international exchanges. Consequently, telehealth networks have assumed pivotal importance during COVID-19 pandemics, particularly for rare and complex diseases requiring highly specialized multidisciplinary teams.

To our knowledge, we proposed the first teleconsulting network between Saudi Arabia and Italy for the management and diagnosis of HCM and complex heart diseases. The HCM-Extended Family Unit consists in a virtual network involving different specialists including cardiologists, cardiac surgeons, geneticists, neurologists, pediatric cardiologists and metabolisms experts aiming to discuss the best management for complex and rare disease of the heart, both in adults and pediatric patients. In addition, the cooperation between Saudi Arabia and Italy aims to provide new scientific perspectives in the understanding of rare cardiovascular diseases, with the creation of shared datasets and digital platforms and multicenter research protocols.

Conclusions

HCM is a relatively rare disease, most of the patients can have a good quality of life but accurate diagnosis starting with the family screening and the identification of phenocopies. The HCM-Family Unit is a "way of working" where health care professionals such as cardiologists, internists, cardiovascular surgeons, geneticists, pediatric cardiologists, nurses, psychologists are involved. Moreover, international cooperation is mandatory given the relatively uncommon/rare disease in order to share knowledge, create a research platform that will undoubtedly improve the quality of health care.

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