Current management of hypertrophic cardiomyopathy

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ABSTRACT

Hypertrophic cardiomyopathy is a common yet under-recognized genetic structural heart condition characterized by left ventricular hypertrophy. Patients may present with obstructive disease characterized by an elevated left ventricular outflow tract gradient or non-obstructive disease. Long established medical and surgical treatment options for patients with obstructive hypertrophic cardiomyopathy and refractory symptoms can be effective in eliminating outflow tract gradients and improving symptoms. Cardiac myosin inhibitors have emerged as a new class of evidence based medical therapy for patients with obstructive hypertrophic cardiomyopathy and an alternative to septal reduction therapies. However, effective treatments for patients with non-obstructive hypertrophic cardiomyopathy remain limited, with several clinical trials ongoing. Variants in cardiac sarcomeric genes are the primary genetic cause of hypertrophic cardiomyopathy and are being investigated as targets for gene based therapies. Stratification of the risk of sudden death is an important component of caring for patients with hypertrophic cardiomyopathy. Recommendations for implantable cardioverter-defibrillator implantation are based on well validated risk factors in combination with shared decision making. Atrial fibrillation is common in patients with hypertrophic cardiomyopathy, and anticoagulation is strongly recommended for stroke prevention. Rhythm control is essential for patients with symptomatic atrial fibrillation. Historically, vigorous exercise has been restricted; however, newer data suggest that the arrhythmic risk is less than previously thought and emphasize an individualized approach. Advanced heart failure is an uncommon but important cause of morbidity and mortality. Early identification is key to improving outcomes with advanced therapies including cardiac transplantation. The management of hypertrophic cardiomyopathy is rapidly evolving toward a more personalized approach, based on genotype and phenotype, to alter disease progression and improve patients' outcomes.

Introduction

Hypertrophic cardiomyopathy is a common yet under-recognized structural heart condition. It has been defined as left ventricular wall thickness of ≥15 mm in any myocardial segment, not explained by alternate conditions leading to increased load, such as hypertension or aortic stenosis, or infiltration, such as amyloidosis. A diagnosis with less significant hypertrophy (≥13 mm) is possible in the context of a corroborating family history or positive genotype.[1] The clinical manifestations are heterogeneous, ranging from asymptomatic disease to sudden cardiac death and advanced disease necessitating heart transplantation.

The bulk of gene variants that cause hypertrophic cardiomyopathy lead to alterations of key aspects of cardiac sarcomere function,[2] with impaired actomyosin cross bridge cycling and subsequent increase in myocyte contractility and ATP utilization.[3 4] Additionally, some hypertrophic cardiomyopathy variants studied to date result in release of myosin heads from a sequestered state, increasing availability for interaction with actin.[5] These stressors ultimately contribute to the characteristic phenotype of hypertrophic cardiomyopathy, which includes myocyte hypertrophy, structural disarray, and myocardial fibrosis.[6]

Initial medical and surgical therapeutic interventions for hypertrophic cardiomyopathy were first described more than 60 years ago.[7] Advances in research during the past decade have ushered in a new era of highly effective and potentially disease modifying therapies, altering the treatment paradigm. Several promising treatments are now in varying stages of development. This review provides a critical analysis of the rapidly evolving and wide ranging therapeutic landscape in hypertrophic cardiomyopathy.

Epidemiology

Hypertrophic cardiomyopathy has a global presence with an estimated prevalence of 1 in 500. It has been described in at least 125 countries and has a similar prevalence in men and women.[8 9] Despite improvements in community awareness and

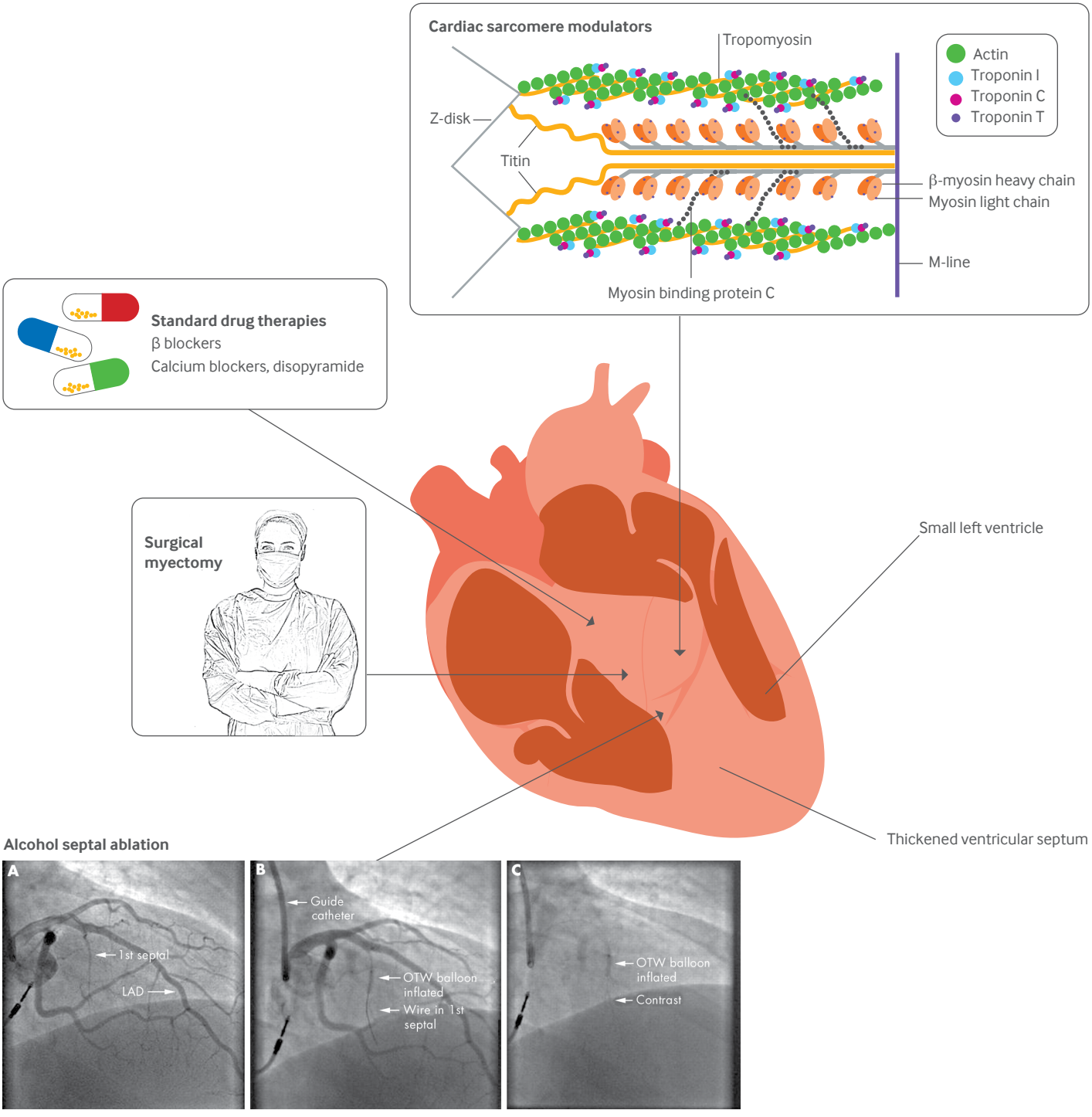


Fig 1 | Treatments for patients with symptomatic obstructive hypertrophic cardiomyopathy. Alcohol ablation image reproduced with permission from *Heart* 2006;92:1339-44

Table 1 | Studies of pharmacological agents for treatment of patients with symptomatic obstructive hypertrophic cardiomyopathy (HCM)

Intervention	Year, author	Study design	Inclusion criteria	No	Follow-up	Outcome
β blocker (propranolol)	1967, Cohen[23]	Non-randomized, prospective, crossover; propranolol *v* placebo	Symptomatic idiopathic subaortic stenosis	7	15 months	4/7 improved exercise tolerance; 3/7 avoided surgical intervention
β blocker (propranolol)	1970, Adelman[24]	Case series	Symptomatic muscular subaortic stenosis	21	24 months	Symptomatic improvement; 4/4 with provocable gradient; 7/17 with obstruction at rest
β blocker (propranolol)	1973, Stenson[25]	Case series	Symptomatic hypertrophic subaortic stenosis	13	17 months	Symptomatic improvement in 7/13; worse outcomes in patients who had severe symptoms
β blocker (TEMPO)	2021, Dybro[26]	Randomized, double blind, placebo controlled, crossover trial	Adults with obstructive HCM with LVOTg >30 mm Hg at rest or 50 mm Hg with Valsalva; NYHA ≥II	29	4 weeks	LVOTg with metoprolol lower *v* placebo. Rest: 25 (IQR 15-58) *v* 72 (28-87) mm Hg; peak exercise: 28 (8-40) *v* 62 (31-113) mm Hg; post-exercise: 41 (24-100) *v* 115 (55-171) mm Hg). After treatment with metoprolol, 14% of patients NYHA ≥III *v* 38% of patients on placebo
Calcium channel blocker (verapamil)	1979, Rosing[27]	Non-randomized, prospective crossover	Symptomatic HCM	19	6 months	Improved exercise capacity 26% short term and 45% at 3.5-6 months; symptom relief 11/15
Calcium channel blocker (verapamil)	1981, Bonow[28]	Prospective case-control	Symptomatic HCM	40	36 hours	Improved diastolic filling in 30/40; no change in systolic function
Calcium channel blocker (diltiazem/verapamil)	1986, Toshima[29]	Prospective, double blind, crossover	Symptomatic HCM	32	14 days	Symptomatic improvement: diltiazem 83%, verapamil 71%; no difference between two CCBs in global improvement or safety
Disopyramide	2005, Sherrid[30]	Retrospective	Obstructive HCM treated with disopyramide	118	3.1 years	Two thirds did not require major non-drug intervention; lower LVOTg; improved NYHA class
Disopyramide	2013, Sherrid[31]	Retrospective	Obstructive HCM	299	4.8 years	60% reduction in resting LVOTg; 2/3 who otherwise would have been candidates did not require SRT
Disopyramide	2017, Adler[32]	Retrospective	HCM on disopyramide initiated in outpatient setting	168	37 months	No cardiac events at 3 months; <0.09% long term cardiac events; 23% stopped medication owing to side effects; 63% remained free of SRT
Cardiac myosin inhibitor: mavacamten (EXPLORER-HCM)	2020, Olivotto[33]	Randomized, double blind, placebo controlled	Adults with obstructive HCM with LVOTg >50 mm Hg, EF >55%, NYHA II-III symptoms	251	30 weeks	Improved functional capacity and symptoms: ≥1.5 mL/kg/min increase in pVO_2 with ≥1 NYHA class improvement or ≥3 mL/kg/min increase in pVo_2 with no worsening of NYHA class 37% mavacamten *v* 17% placebo (difference 19.4, 95% CI 8.7 to 30.1)
Cardiac myosin inhibitor: mavacamten (MAVA-LTE)	2024, Rader[34]	Long term extension of EXPLORER-HCM study	Adults with obstructive HCM with LVOTg >50 mm Hg, EF >55%, NYHA II-III symptoms	231	60 weeks	Mean change in LVOTg on mavacamten −35.6 (SD 32.6) mm Hg at week 48 and −32.8 (30.8) mm Hg at week 84. Mean change in pro-BNP from baseline at week 48: −480 (IQR −1104 to −179) ng/L); mean change in EF from baseline through week 48 −7.0% (SD 8.3%)
Cardiac myosin inhibitor: mavacamten (VALOR-HCM)	2024, Desai[35]	Randomized, double blind, placebo controlled with crossover at 16 weeks	LVOTg >50 mm Hg, NYHA III-IV despite maximally tolerated medical therapy, EF >60%	112	128 weeks	Mavacamten decreased need or eligibility for SRT. At 16 weeks: 76.8% of patients on placebo and 17.9% of those on mavacamten met criteria for SRT (difference 58.9%, CI 44% to 73.9%). At 128 weeks, 15.7% patients in total study sample (108 patients) met composite endpoint
Cardiac myosin inhibitor: aficamten (SEQUOIA-HCM)	2024, Maron[36]	Randomized, double blind, placebo controlled	LVOTg >30 mm Hg at rest or 50 mm Hg with exercise, NYHA II-III symptoms, EF >60%	282	24 weeks	Aficamten showed improvement in peak oxygen uptake compared with placebo. Aficamten: 1.8 (95% CI 1.2 to 2.3) mL/kg/min; placebo: 0.0 (−0.5 to 0.5). mL/kg/min

BNP=B-type natriuretic peptide; CCB=calcium channel blocker; CI=confidence interval; EF=ejection fraction; IQR=interquartile range; LVOTg=left ventricular outflow tract gradient; NYHA=New York Heart Association; SD=standard deviation; SRT=stereotactic radiotherapy.

advances in screening, an estimated 80-90% of cases remain undiagnosed.[10 11] Depending on the cohort studied, 30-60% of patients harbor genetic variants inherited as autosomal dominant traits, whereas no pathogenic variant is identified in around 40%.[12] Although overall mortality has decreased over the past several decades, sex, age, and race/ethnicity related disparities in long term outcomes persist.[13] Women with the disease have higher rates of heart failure and mortality.[14]

Sources and selection criteria

We identified source literature through searches of PubMed and Medline using search terms "hypertrophic cardiomyopathy" AND [one of] "medications, [including specifics] myectomy, septal reduction, sudden death, defibrillator, atrial fibrillation, heart failure". We scanned bibliographies of relevant publications for further relevant studies. We predefined the priority of studies to be included on the basis of quality: For therapies for which randomized clinical trials are available, we prioritized these. For those for which only non-randomized (or crossover) studies exist, we included these. As much literature supporting guideline indicated therapies in hypertrophic cardiomyopathy has been in existence for many years, we did not set a start time for the search, conducted most recently in September 2024.

Initial medical therapy

Obstructive disease

Assessment

Obstructive hypertrophic cardiomyopathy is characterized by left ventricular outflow tract

Table 2 | European and US guidelines on hypertrophic cardiomyopathy (HCM)

Recommendation	2023 ESC guidelines (class)	2024 ACC/AHA guidelines (class)
Medical management		
Non-dilating β blockers recommended as first line therapy for symptomatic LVOTO	I	I
Non-dihydropyridine CCBs recommended for symptomatic LVOTO in patients intolerant of or unable to receive β blockers	I	I
Cardiac myosin inhibitors recommended for patients with symptomatic LVOTO despite first line therapy	II	I
Disopyramide recommended for patients with symptomatic LVOTO despite first line therapy	I	I
Invasive management		
SRT recommended as treatment in symptomatic LVOTO >50 mm Hg and NYHA II-IV symptoms despite maximally tolerated medical therapy	I	I
Diagnosis		
Cardiac MRI indicated in patients with suspected cardiomyopathy as part of initial evaluation	I	NA
Cardiac MRI indicated in patients with suspected HCM when echocardiography is inconclusive or suspicion for alternative diagnosis exists	NA	I
Sudden cardiac death		
ICD recommended for survivors of sudden cardiac death or hemodynamically significant VT	I	I
For patients with HCM and ≥1 risk factor, estimation of 5 year risk of sudden death can be useful in shared decision making process for ICD placement	NA	II
HCM-SCD risk calculator is recommended for sudden cardiac death at 5 years in patients ≥16 years old	I	NA
Atrial fibrillation		
Oral anticoagulation recommended in all patients with atrial fibrillation or flutter, regardless of CHADS-VASC score	I	I
Rhythm control strategy with AAD or cardioversion recommended in patients with poorly tolerated AF	NA	II
Rhythm control should be considered at an early stage of disease regardless of symptoms	II	NA
Catheter ablation recommended as rhythm control strategy for symptomatic AF when drugs are ineffective or not tolerated or on basis of patient preference	I	II
Exercise and competitive athletics		
Mild-to-moderate exercise recommended for all individuals	I	I
For athletes, comprehensive evaluation, individualized risk assessment, and shared decision making about sports participation with expert professional recommended	I	I
Advanced heart failure		
In patients with EF <50% and LBBB and NYHA II-IV symptoms despite GDMT, CRT can be beneficial to improve symptoms	Recommend standard criteria for CRT	II

AAD=anti-arrhythmic drug; ACC=American College of Cardiology; AF=atrial fibrillation; AHA=American Heart Association; CCB=calcium channel blocker; CRT=cardiac resynchronization therapy; ESC=European Society of Cardiology; EF=ejection fraction; GDMT=guideline directed medical therapy; ICD=implantable cardioverter-defibrillator; LBBB=left bundle branch block; LVOTO=left ventricular outflow tract obstruction; MRI=magnetic resonance imaging; NA=not applicable; NYHA=New York Heart Association; SCD=sudden cardiac death; VT=ventricular tachycardia

(LVOT) obstruction, with a peak instantaneous Doppler echocardiography gradient of ≥30 mm Hg, although the predicted threshold at which this gradient becomes hemodynamically significant is ≥50 mm Hg at rest or with physiologic provocation.[15] Echocardiography with provocative maneuvers including Valsalva and exercise is important in determining the presence of obstruction, as only one third of patients with hypertrophic cardiomyopathy have outflow tract obstruction at rest.[16] The degree of LVOT gradients measured varies considerably depending on the patient's position, method of exercise, time of day, and volume status.[17 18]

Treatment

Figure 1 shows options for treatment of symptomatic obstructive hypertrophic cardiomyopathy. Initiation and titration of medical therapy in obstructive hypertrophic cardiomyopathy should focus on symptom management. To date, no data suggest that any current medical therapy improves survival. Similarly, no data support initiation of gradient reduction therapy in patients without symptoms.

An important and frequently overlooked initial step is a review of drug treatments that may worsen LVOT obstruction. These include many of the drugs commonly prescribed for hypertension such as dihydropyridine calcium channel blockers (CCBs), angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and diuretics. Nitrates or phosphodiesterase type 5 inhibitors may reduce preload and promote vasodilation, worsening obstruction.[19] Use of these drugs should be limited if possible. Also, all patients should be counseled on lifestyle modifications including avoidance of dehydration, large or carbohydrate rich meals, and caffeine. Alcohol use has been shown to increase LVOT obstruction and should be minimized [20-22]

Table 1 shows studies of drug treatments for patients with symptomatic obstructive hypertrophic cardiomyopathy. Despite a paucity of randomized data, on the basis of data from series and crossover studies, non-vasodilating β blockers and CCBs remain the first line treatments for symptomatic hypertrophic cardiomyopathy.[22] β blockers were first described in the 1960s by Eugene Braunwald as treatment for "idiopathic hypertrophic subaortic stenosis" [23] and subsequently became established as first line therapy. Non-vasodilating β blockers (metoprolol, atenolol, bisoprolol, and nadolol) are preferred. The only randomized trial of these agents, a small, crossover randomized controlled trial (RCT), showed that compared with placebo, metoprolol significantly reduced LVOT gradient (P<0.01), and improved quality of life (Kansas City Cardiomyopathy Questionnaire; P<0.04). Metoprolol did not improve

Table 3 | Notable negative randomized controlled trials in hypertrophic cardiomyopathy (HCM)

Intervention	Year, author	Study design	Inclusion criteria	No	Follow-up	Outcome
Trimetazidine	2019, Coats[42]	Randomized, double blind, placebo controlled	Non-obstructive HCM (LVOTg <50 mm Hg)	49	3 months	No difference in peak VO_2 between trimetazidine and placebo
Ranolazine	2018, Olivotto[43]	Randomized, double blind, placebo controlled	Non-obstructive HCM (LVOTg <30 mm Hg), NYHA II or III symptoms	80	5 months	No difference in peak VO_2 between ranolazine and placebo
Atorvastatin	2016, Hersi[44]	Randomized, placebo controlled	Obstructive or non-obstructive HCM	22	12 months	No difference in LV mass (by cMRI) between atorvastatin and placebo
Losartan	2015, Axelsson[45]	Randomized, double blind, placebo controlled	Obstructive or non-obstructive HCM	133	12 months	No difference in LV mass between losartan and placebo

cMRI=cardiac magnetic resonance imaging; LV=left ventricular; LVOTg=left ventricular outflow tract gradient; NYHA=New York Heart Association.

exercise capacity or peak oxygen consumption or lower brain natriuretic peptide.[26] The use of non-vasodilating β blockers as first line therapy is a class I recommendation in the 2024 American College of Cardiology (ACC)/American Heart Association (AHA) and 2023 European Society of Cardiology (ESC) guidelines (table 2).[1 22]

Non-dihydropyridine CCBs (diltiazem or verapamil) are used when β blockers are contraindicated or poorly tolerated. Older data suggest short term improvements in symptoms and exercise capacity.[27 29] They should be used with caution in patients with heart failure or LVOT gradient >100 mm Hg given the risk of pulmonary edema.[37] Both the 2024 ACC/AHA and 2023 ESC guidelines give non-dihydropyridine CCBs a class I recommendation for patients in whom β blockers are ineffective or not well tolerated (table 2).[1 22] β blockers and CCBs are sometimes combined in patients with refractory symptoms, although no substantial evidence supports this practice and it does not appear in the guidelines. Combination therapy should be started with close monitoring of heart rate and blood pressure.

Patients who do not respond to initial medical therapy

Disopyramide, a class IA anti-arrhythmic with negative inotropic effects, has historically been the next choice in patients who do not respond to initial medical therapy. Disopyramide has been shown in retrospective studies to be safe and associated with an improvement in both LVOT gradient and symptoms when used in combination with β blockers or non-dihydropyridine CCBs. Use requires monitoring of the QTC interval and can be associated with anticholinergic symptoms.[30 31] As described below, increasing data suggest that cardiac myosin inhibitors are an appropriate second line therapy if first line agents are not successful at reducing symptoms.

Management of acute hypotension

In the absence of randomized data, recommendations for management of acute hypotension are based on physiologic principles and expert consensus. Patients with obstructive hypertrophic cardiomyopathy and LVOT obstruction are less likely to tolerate hemodynamic changes associated with increased contractility or reduced preload and afterload. When these patients are admitted to hospital or undergoing surgical procedures, expeditious management of hypotension is important. Adequate preload should be maintained with appropriate fluid resuscitation. If vasopressors are required, an α blocker such as phenylephrine should be used. In a monitored setting, β blockers can be used in combination with vasoconstrictors to reduce contractility and prolong diastolic filling, improving LVOT obstruction.[38]

For patients who develop clinical evidence of volume overload, low dose diuretics can be cautiously started. Given the potential for preload reduction and resultant worsening of LVOT obstruction, the minimal effective dose should be targeted and ongoing use should be periodically reassessed.[39]

Non-obstructive disease

Many patients with non-obstructive hypertrophic cardiomyopathy have symptoms, with 8% in New York Heart Association (NYHA) class III or IV, and mortality rates are similar to those of patients with obstructive hypertrophic cardiomyopathy.[40] Limited evidence exists to guide medical therapy for these patients. Current management of dyspnea in patients with non-obstructive hypertrophic cardiomyopathy is limited to diuretics for symptomatic heart failure. On the basis of data from the phase 2 VANISH RCT, valsartan may attenuate adverse cardiac remodeling in younger patients (<45 years) with early stage disease and pathogenic or likely pathogenic sarcomeric variants and can be considered in this selected population.[41] At the other end of the spectrum, patients who progress to symptomatic heart failure with reduced ejection fraction should be managed with appropriate guideline directed medical therapy as for heart failure with reduced ejection fraction of other causes and should prompt an evaluation for advanced therapies, discussed later in this review.

Additional medical therapies

Several additional medical therapies have been shown in RCTs to be ineffective in obstructive and non-obstructive hypertrophic cardiomyopathy, summarized in table 3.

Cardiac myosin inhibitors

The most meaningful recent progress in the treatment of hypertrophic cardiomyopathy has been the development of cardiac myosin inhibitors (CMIs). The first in class CMI is mavacamten, an orally

administered selective inhibitor of cardiac myosin adenosine triphosphatase (ATPase). It has been approved by several regulatory agencies, including in the US, the UK, Europe, Switzerland, Singapore, South Korea, and Brazil. Inhibition of cardiac myosin ATPase results in reduced availability of myosin heads for engagement in actin-myosin cross bridging, a key interaction in cardiac contraction. This is thought to be effective because myocardial hypercontractility is a key component of the pathophysiology of hypertrophic cardiomyopathy.[46]

Use of mavacamten in obstructive hypertrophic cardiomyopathy is supported by the phase 3 RCT EXPLORER-HCM,[33] which evaluated the effect of mavacamten on peak exercise capacity and NYHA class. The study enrolled 251 patients with an LVOT gradient ≥50 mm Hg, NYHA II-III symptoms, and an ejection fraction of ≥55%, with a 30 week treatment period with either mavacamten or placebo. The primary outcome (≥1.5 mL/kg/min increase in pVO_2 with at least one NYHA class improvement or ≥3.0 mL/kg/min increase in pVO_2 with no worsening of NYHA class at 30 weeks) occurred in 37% of the mavacamten group compared with 17% of the placebo group (P=0.0005). Mavacamten was associated with a significant reduction in LVOT gradient and improvement in quality of life as measured by the Kansas City Cardiomyopathy Questionnaire, compared with placebo.[47] A magnetic resonance imaging (MRI) sub-study showed that mavacamten had a favorable effect on cardiac remodeling; specifically, significant reductions in absolute intracellular myocardial mass index as well as left ventricular mass index, maximum left ventricular wall thickness, and left atrial volume index were seen.[48] Patients in the EXPLORER-HCM cohort are being followed in a long term extension study (MAVA-LTE) evaluating LVOT gradient, NYHA class, and N-terminal pro B-type natriuretic peptide (nt-proBNP) concentrations, with durability of treatment response at 180 weeks.[49]

The subsequent VALOR-HCM trial enrolled 112 patients with obstructive hypertrophic cardiomyopathy who were NYHA class III and being considered for septal reduction therapy (SRT), and randomized patients to mavacamten or placebo for 16 weeks. Patients receiving mavacamten experienced improvement in symptoms and reduction in need for SRT from 76.8% of the placebo group to 17.9% of those treated with mavacamten (confidence interval for difference 44 to 74). This benefit persisted up to 128 weeks and included patients from the placebo arm who crossed over to mavacamten at the end of the randomized study period.[50] These data suggest that in appropriately selected patients with severe symptoms, CMIs can be considered as an alternative to SRT.

Aficamten, the second in class CMI, was tested in the recently published SEQUOIA-HCM RCT. This study randomized 282 patients with symptomatic obstructive hypertrophic cardiomyopathy and LVOT gradients ≥50 mm Hg to aficamten or placebo. Patients receiving aficamten showed significantly improved peak VO_2 (1.8 mL/min/kg improvement, compared with 0.0 mL/min/kg in patients receiving placebo; P<0.001 for between group difference), with similar low rates of adverse events (5.6% in aficamten group, none thought to be due to drug, versus 9.3% for placebo).[36] Aficamten is currently under review by regulatory agencies.

As participants in these CMI trials were maintained on β blockers, CCBs, and disopyramide, whether CMIs could be used as first line therapy in patients with symptomatic obstructive hypertrophic cardiomyopathy is unclear. A phase 3 clinical trial comparing metoprolol succinate and aficamten (CY 3773274) in patients with symptomatic obstructive hypertrophic cardiomyopathy and LVOT obstruction is expected to complete enrollment in 2025.[51] Most (75%) patients in EXPLORER and MAVA-LTE received β blockers. Concurrent β blocker use did not affect functional capacity, reduction in LVOT gradients, symptoms, or biomarkers, but patients on β blockers had lower peak VO_2 and chronotropic incompetence.[52] The 2023 ESC guidelines assigned a class 2a recommendation to use of CMIs in patients with symptomatic hypertrophic cardiomyopathy with LVOT obstruction, in addition to β blockers or CCBs or as monotherapy when β blockers, CCBs, or disopyramide are not tolerated or contraindicated, before considering SRT.[1] The 2024 AHA/ACC guidelines give a class 1 recommendation to the use of CMIs, disopyramide, or SRT in patients who have symptoms despite first line therapy (table 2).[22]

Important considerations with CMIs

Several considerations are important as CMI use increases. The potential for development of systolic dysfunction with potential for heart failure, although rare, requires frequent echocardiographic monitoring. In the EXPLORER trial, 5.6% of patients on mavacamten compared with 1.5% on placebo had a transient drop in ejection fraction to <50% during the trial, requiring treatment discontinuation and resumption at a lower dose.[33] This is like the rate in SEQUOIA-HCM in which 3.5% of patients on aficamten versus 0.7% of patients on placebo had a transient drop in ejection fraction to <50%.[36] Declines in ejection fraction to <50% have continued to be observed in the long term extensions of these trials. In EXPLORER-LTE, the number of patients with drop in ejection fraction to <50% was 8.7%,[49] and in VALOR-LTE it was 15.7%,[50] although clinical heart failure was much less common. “Real world” data from the Risk Evaluation and Mitigation Strategy (REMS) database, although not adjudicated, have shown a reduction in ejection fraction to <50% in 4% of patients and clinical hospital admission for heart failure in <1% of patients.[53] Therefore, continued long term surveillance of patients on stable doses of CMIs is warranted.

Whether CMIs are associated with an increased rate of atrial fibrillation is not yet determined. A single center report described an increased incidence

of atrial fibrillation in patients after treatment with mavacamten compared with before treatment, but these patients had a high rate of baseline atrial fibrillation.[54] In the long term follow-up MAVA_LTE,[49] the incidence of atrial fibrillation adjusted for exposure was 4.5%. A recent meta-analysis of CMI trials did not show an increase in atrial fibrillation.[55]

Several dose adjustments may be needed, and CYP2C19 genotyping is required in the UK to determine the initial dose.[56] In the US, mavacamten is available only through a Food and Drug Administration mandated REMS that requires enrollment and education of prescribers and patients, as well as data uploading and pharmacy certification. This program currently mandates echocardiograms every four weeks during drug initiation and every 12 weeks during drug maintenance.

A randomized clinical trial in children with obstructive hypertrophic cardiomyopathy is under way (CEDAR-HCM). Use of CMIs in pregnant patients is contraindicated owing to possible teratogenic effects. The published CMI trials enrolled patients with limited racial and ethnic diversity, so how generalizable the benefits will be to patients who come from under-represented backgrounds is unclear.[57] Potential long term cost burden to payers and patients, as well as the cost effectiveness of CMI therapy in comparison with established therapies, could limit the extent of adoption.[58] Forthcoming prospective studies from long term trial extensions and clinical use will be useful in answering these questions.

Invasive approaches to therapy

Obstructive disease

Invasive treatment with SRT is typically reserved for patients with NYHA III or IV symptoms and LVOT gradient ≥50 mm Hg who have not responded favorably to medical therapy. SRT was initially done more than 60 years ago with open surgical partial resection of the hypertrophied interventricular septum. In centers with experienced operators, it is associated with an improvement in symptoms in 90-95% of patients and a mortality rate of <1%.[59] Retrospective studies have suggested that patients with LVOT obstruction who undergo septal reduction have lower mortality than those who have medical treatment,[60 61] but as these are non-randomized the role of referral bias cannot be determined. Postoperative atrial fibrillation and increasing age are associated with worse short term outcomes.[62] Patients who have intrinsic mitral valve disease are unlikely to improve with SRT alone and should be considered for mitral valve intervention at the time of surgery. Mitral valve repair is preferred to replacement and is associated with improved survival.[63]

Catheter based alcohol septal ablation (ASA) was initially described in a series of patients at Royal Brompton Hospital in 1994.[64] ASA and septal myectomy have comparable rates of 30 day survival, sudden cardiac death, and long term survival in published studies, although no RCT has ever been done. A retrospective comparison suggested improved mortality with myectomy over ASA, but referral bias cannot be excluded.[65] ASA is associated with higher rates of post-procedural pacemaker implantation and has a significantly higher risk of re-intervention compared with patients undergoing surgery.[66] In appropriately selected patients, the procedure is associated with an improvement in NYHA class, five year survival free from cardiovascular events of 98.6%, and 10 year survival free from cardiovascular events of 92.3%.[67] In a long term multinational cohort of patients undergoing ASA, all cause mortality was independently associated with reduction in LVOT gradient.[68]

The 2024 AHA/ACC hypertrophic cardiomyopathy guidelines suggest CMIs, disopyramide, and SRT as potential options for patients with refractory symptoms despite maximal β or calcium channel blockade. When considering invasive therapy, a multidisciplinary and shared decision making approach with the patient is essential. Key factors that should be considered are the patient's specific anatomy, coexistent pathology, surgical risk, and comorbidities, as well as the center's expertise and the patient's preference.

Non-obstructive disease

A small subset of patients with extensive apical hypertrophic cardiomyopathy, a small left ventricular cavity, and severely limiting symptoms may be considered for apical myectomy, done in a few highly specialized centers. In a single center study, apical myectomy increased stroke volume and improved postoperative measurements of left ventricular compliance.[69] Most patients with non-obstructive hypertrophic cardiomyopathy and refractory symptoms from heart failure despite treatment with guideline directed medical therapy should be considered for heart transplantation or advanced therapies if eligible.

Hypertrophic cardiomyopathy genetics

Genotype positive hypertrophic cardiomyopathy

Variants in genes that encode for myofilament proteins of the cardiac sarcomere are found in 30-50% of patients with hypertrophic cardiomyopathy.[70-74] These variants show autosomal dominant inheritance, variable expressivity, and age related penetrance. To date, variants in eight different sarcomeric genes have been identified as definitively causative of hypertrophic cardiomyopathy, and variants in several other genes show at least moderate evidence of pathogenicity (table 4; fig 2).[75-77] The most common of the sarcomeric gene variants in hypertrophic cardiomyopathy are those affecting the thick filament proteins cardiac myosin binding protein C (*MYBPC3*) and β-myosin heavy chain (*MYH7*). Less common are variants in genes affecting the thin filament sarcomeric proteins troponin T (*TNNT2*), troponin I (*TNNI3*), tropomyosin 1 (*TPM1*), and α-cardiac actin (*ACTC1*), as well as the thick filament proteins myosin regulatory light

Table 4 | Genes and phenocopies involved in hypertrophic cardiomyopathy (HCM)

Gene	Affected protein	Estimated HCM frequency	Characteristics
Sarcomere genes with definitive HCM pathogenicity			
MYBPC3	Cardiac myosin binding protein-C	14-26%	Thick filament protein; binds to MYH7 and actin to regulate actomyosin interactions
MYH7	Cardiac b-myosin heavy chain	13-25%	Thick filament protein; binds ATP and actin, essential for contraction
TNNT2	Cardiac troponin T	4-15%	Thin filament protein; anchors troponin complex to tropomyosin
TNNI3	Cardiac troponin I	2-7%	Thin filament protein; inhibitory component of troponin/tropomyosin complex
TPM1	Tropomyosin 1	<5%	Thin filament protein; binds to troponin complex to regulate actin/myosin interactions
ACTC1	a-cardiac actin	Rare	Thin filament protein; interacts with troponin/tropomyosin and MYH7 to generate force
MYL2/MYL3	Myosin regulatory light chain/myosin essential light chain	Rare	Thick filament proteins; interact with MYH7 protein to regulate contractility
Additional genes with probable HCM pathogenicity (sarcomere, sarcomere related, and non-sarcomere)			
TNNC1	Cardiac troponin C	Rare	Thin filament protein; calcium sensing component of troponin/tropomyosin complex
ACTN2	a-Actin 2	Rare	Z line protein; binds to actin, regulates sarcomere function; mutations associated with skeletal myopathy and various cardiomyopathies
CSRP3	Cysteine and glycine rich protein 3 (muscle LIM protein)	Rare	Z line protein; links contractile apparatus to sarcolemma; mutations typically not sufficient to cause HCM, but complement other genes in pathogenesis
TRIM63	E3 ubiquitin-protein ligase TRIM63 (muscle ring-finger protein-1, MuRF-1)	Rare	M line protein; tags thick filament proteins for degradation; autosomal recessive inheritance
KLHL24	Ubiquitin ligase substrate receptor Kelch-like protein 24	Rare	Mediates protosomal degradation of intermediate filaments; loss of function: hypertrophic phenotype with desmin overload, gain of function: dilated phenotype with skin fragility
FHOD3	FH1/FH2 domain-containing protein 3	Rare	Probable role in actin filament polymerization; mutations associated with hypertrophic and dilated phenotypes
ALPK3	a-Protein kinase 3	Rare	Sarcomere associated protein; implicated in myocyte differentiation
FLNC	Filamin C	Rare	Sarcomere associated protein; interacts with actin, presumed to regulate cytoskeletal stress responses; more commonly associated with DCM
PLN	Phospholamban	Rare	Regulator of Ca^{2+} homeostasis in cardiac myocytes; more commonly associated with DCM
JPH2	Junctophilin 2	Rare	Junctional membrane protein that regulates Ca^{2+} homeostasis and excitation-contraction coupling
Non-HCM causes of LV hypertrophy (HCM phenocopies)			
GLA	a-galactosidase A (Fabry disease)	–	X linked glycolipid storage disease; LV hypertrophy and fibrosis, valvular disease, arrhythmias, conduction abnormalities, peripheral neuropathy, progressive renal dysfunction, stroke
Ras-MAPK genes	Various Ras/MAPK associated proteins (eg, Noonan and Costello syndromes)	–	Facial dimorphism, short stature, congenital heart disease; ~20% develop LV hypertrophy
PRKAG2	γ-2 regulatory subunit of adenosine monophosphate activated protein kinase	–	Modulates glucose uptake/glycolysis; LV hypertrophy with ventricular pre-excitation, atrial/ventricular arrhythmias, skeletal myopathy, progressive systolic and conduction system dysfunction
LAMP2	Lysosome associated membrane protein 2 (glycogen storage disease IIb, Danon disease)	–	Semidominant X linked disorder; cardiomyopathy (hypertrophic/dilated), ventricular pre-excitation, intellectual disability, skeletal myopathy
TTR (mutant and wild type forms)	Systemic amyloidosis (most commonly transthyretin (ATTR) or light chain (AL))	–	Cardiomyopathy (LV hypertrophy with early diastolic and late systolic dysfunction), arrhythmias, renal dysfunction, peripheral neuropathy, autonomic dysfunction
FXN	Friedreich's ataxia	–	Autosomal recessive; progressive neurological dysfunction (ataxia, dysarthria), often associated with LV hypertrophy, arrhythmias, conduction defects
RAAS polymorphisms	Renin-angiotensin system polymorphisms	–	May contribute to variability in prevalence/ degree of hypertrophy with certain HCM gene mutations (particularly in *MYBPC3* variants)

DCM=dilated cardiomyopathy; LV=left ventricular; MAPK=mitogen activated protein kinase.
Adapted from Walsh,[75] Marian,[76] and Mazzaroto.[77]

chain (*MYL2*) and myosin essential light chain (*MYL3*). Most pathogenic variants in hypertrophic cardiomyopathy are missense with dominant negative effects, although haploinsufficiency related to truncating variants (nonsense, frameshift, and splice site) is the prevailing mechanism in hypertrophic cardiomyopathy related to *MYBPC3*.[78] Variants in genes affecting additional proteins in the sarcomere as well as sarcomere associated proteins and those affecting calcium homeostasis have also been recognized as rare causes of hypertrophic cardiomyopathy.[75]

Studies suggest that phenotypic and outcome based differences exist between the various hypertrophic cardiomyopathy genotypes.[79-81] However, genotype-phenotype correlations in hypertrophic cardiomyopathy are generally modest, with significant phenotypic heterogeneity among patients with similar genetics. Patients with multiple pathogenic variants tend to have more severe phenotypes and earlier ages of presentation.[74 82] The phenotypic heterogeneity among patients with similar gene variants likely relates, in part, to the effect of functional "modifier" variants in other genes that influence the penetrance and phenotypic expression of the main pathogenic variants.[83] In addition to some predictive value, genetic status is useful for family screening

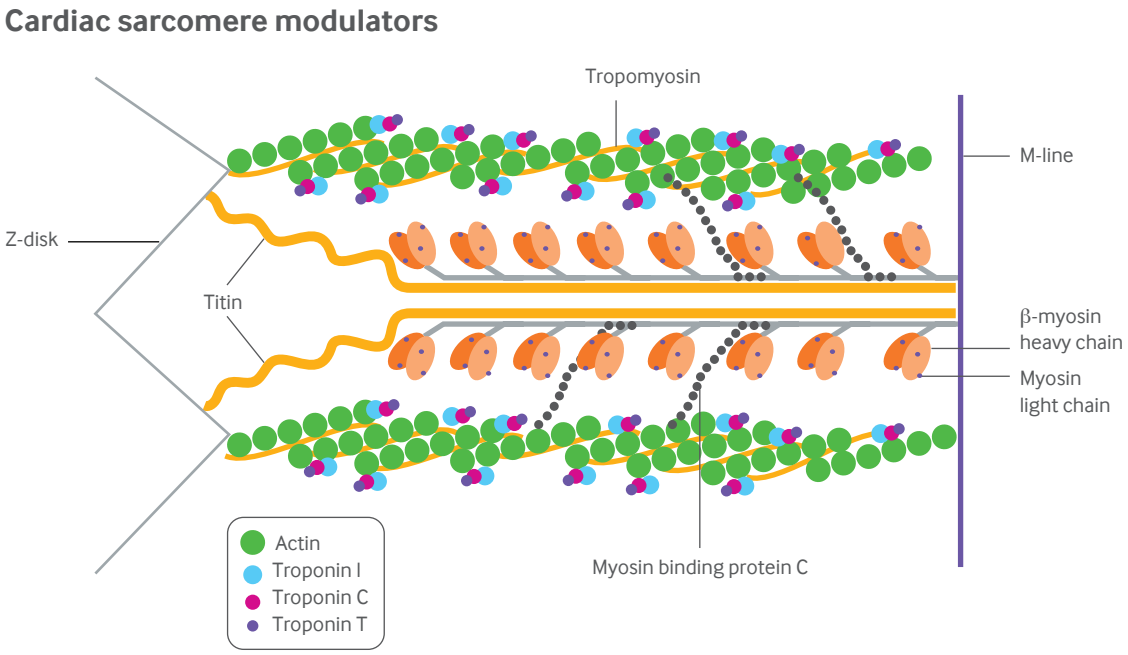


Fig 2 | Genetic underpinnings of hypertrophic cardiomyopathy

Gene elusive hypertrophic cardiomyopathy

The remaining 50-70% of patients with hypertrophic cardiomyopathy who meet clinical diagnostic criteria but do not possess identifiable pathogenic or likely pathogenic gene variants are characterized as "gene elusive." Increasingly, a polygenic contribution to hypertrophic cardiomyopathy is recognized in these patients. Several studies have shown that patients with gene elusive hypertrophic cardiomyopathy tend to present at later ages than their genotype positive counterparts and have milder disease, a lower rate of family history of hypertrophic cardiomyopathy, and better outcomes by multiple metrics,[72 73 84 85] although one study did not find that genotype influenced clinical course.[86] Overall, the prevalence of hypertrophic cardiomyopathy in relatives of patients with gene elusive disease is less than in those with gene positive disease. Recent studies report hypertrophic cardiomyopathy prevalences of 5% and 12% among living relatives within three generations of probands with gene elusive hypertrophic cardiomyopathy,[70 87] compared with 18% in relatives of probands with genotype positive hypertrophic cardiomyopathy and 24% and 37% in relatives with positive genetics.[87-89]

Although novel sarcomeric gene variants that have yet to be identified may account for some gene elusive cases of hypertrophic cardiomyopathy, extensive efforts to find these "missing genes" have thus far identified a limited number of genes that contribute to only a very small proportion of total cases. Overall, these observations suggest that gene elusive hypertrophic cardiomyopathy is largely a phenotypically distinct entity that is most often non-familial with non-mendelian inheritance.

Proposed genetic bases for gene elusive hypertrophic cardiomyopathy include oligogenic and polygenic models related to the combined effects of multiple rare and common genetic variants, as well as complex disease models relating to interactions between common gene variants and non-genetic factors such as hypertension and obesity.[76 77] Genome-wide association studies suggest a strong polygenic influence in hypertrophic cardiomyopathy, especially in sarcomeric negative disease.[90] Analyses of the non-coding regions of the genome may reveal further mechanisms of pathogenicity in gene elusive hypertrophic cardiomyopathy. For example, whole genome sequencing has identified pathogenic variants in deep intronic regions,[91] hypothesized as possibly pathogenic and requiring further research.

Hypertrophic cardiomyopathy phenocopies

Importantly, every evaluation for hypertrophic cardiomyopathy should also reasonably exclude other non-sarcomeric causes of left ventricular hypertrophy, such as infiltrative or metabolic conditions (table 4). These conditions are typically referred to as "hypertrophic cardiomyopathy phenocopies" or "hypertrophic cardiomyopathy mimics" because of their phenotypic overlap with hypertrophic cardiomyopathy. Standard genetic cardiomyopathy panels typically screen for most of the metabolic conditions, which are relatively rare, as well as inherited transthyretin amyloidosis. The presence of extracardiac disease such as neuropathy, skeletal myopathy, or renal disease should raise suspicion for an alternative cause of left ventricular hypertrophy, as the effects of sarcomeric hypertrophic cardiomyopathy are isolated to the heart. Cardiac MRI can be used in conjunction with genetic testing

to differentiate causes of left ventricular hypertrophy and is an ACC/AHA class 1 recommendation in this setting.[92]

Risk assessment for sudden death, US and Europe

Arrhythmic sudden cardiac death and heart failure represent the two most common modes of death related to hypertrophic cardiomyopathy, with an overall low annual mortality rate in contemporary community based populations of 1.5-2%.[93] Efficacy of the implantable cardioverter-defibrillator (ICD) for primary prevention in patients with hypertrophic cardiomyopathy was first reported in 2000,[94] and the decrease in hypertrophic cardiomyopathy related mortality, from 3-6% a year in early cohorts to the current 0.5% year,[95] has been attributed in part to the increasing identification of patients with hypertrophic cardiomyopathy at risk for sudden death with subsequent ICD implantation.[95] Although ICDs save lives, they are not without complications,[96 97] so identification of patients whose risk is high enough that an ICD will provide benefit outweighing the risks is imperative.

Indications for consideration of ICD implantation vary between the US and European guidelines (table 2, fig 3, and fig 4). No randomized trials have evaluated the use of ICDs for primary prevention in hypertrophic cardiomyopathy, so guidelines are based on series showing risk predictors in this population. US guidelines primarily take a dichotomized, algorithmic approach,[22] whereas the European guidelines advise use of the HCM Risk-SCD calculator,[1] initially validated in 2013.[98] As this calculator does not take into consideration all

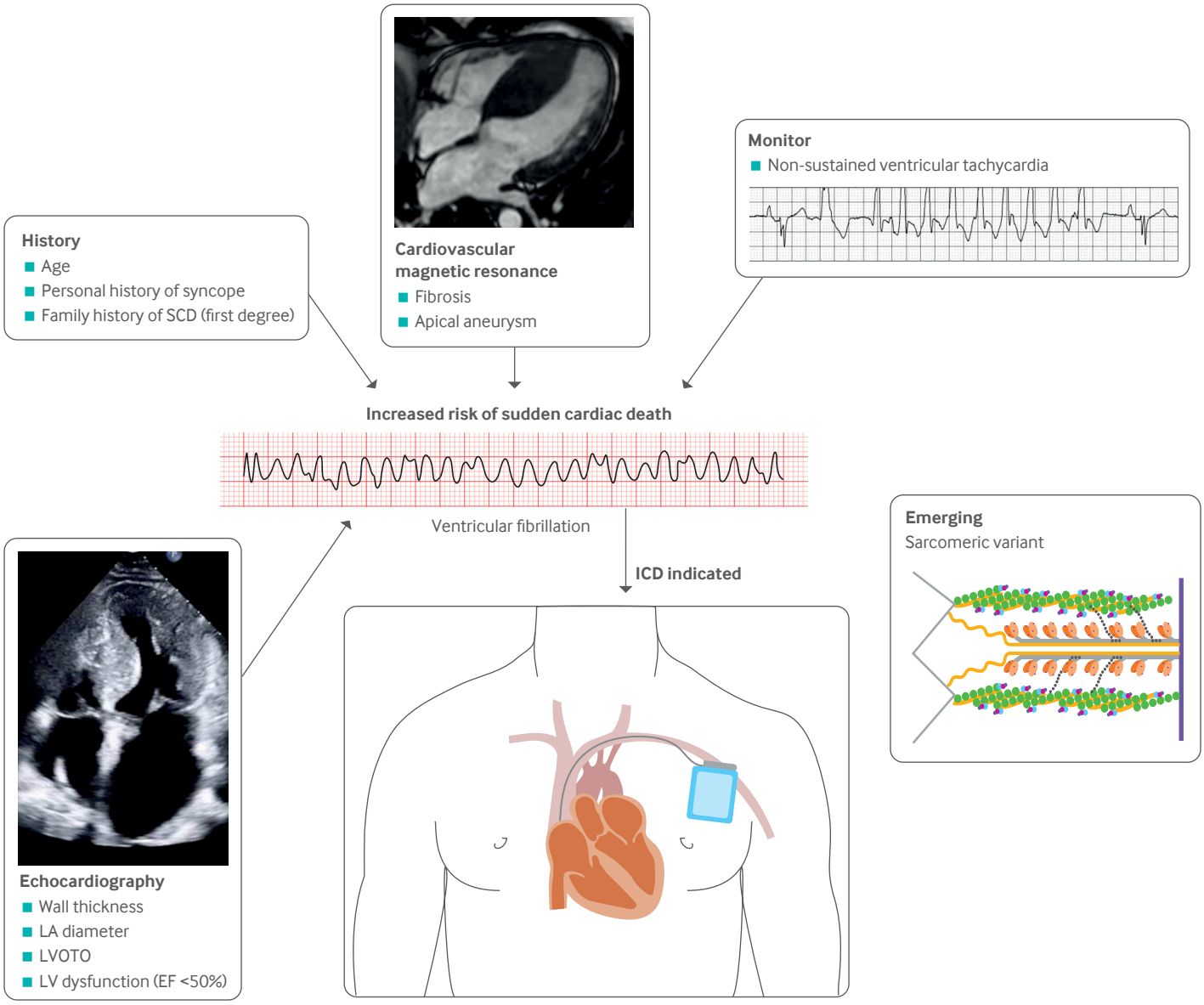
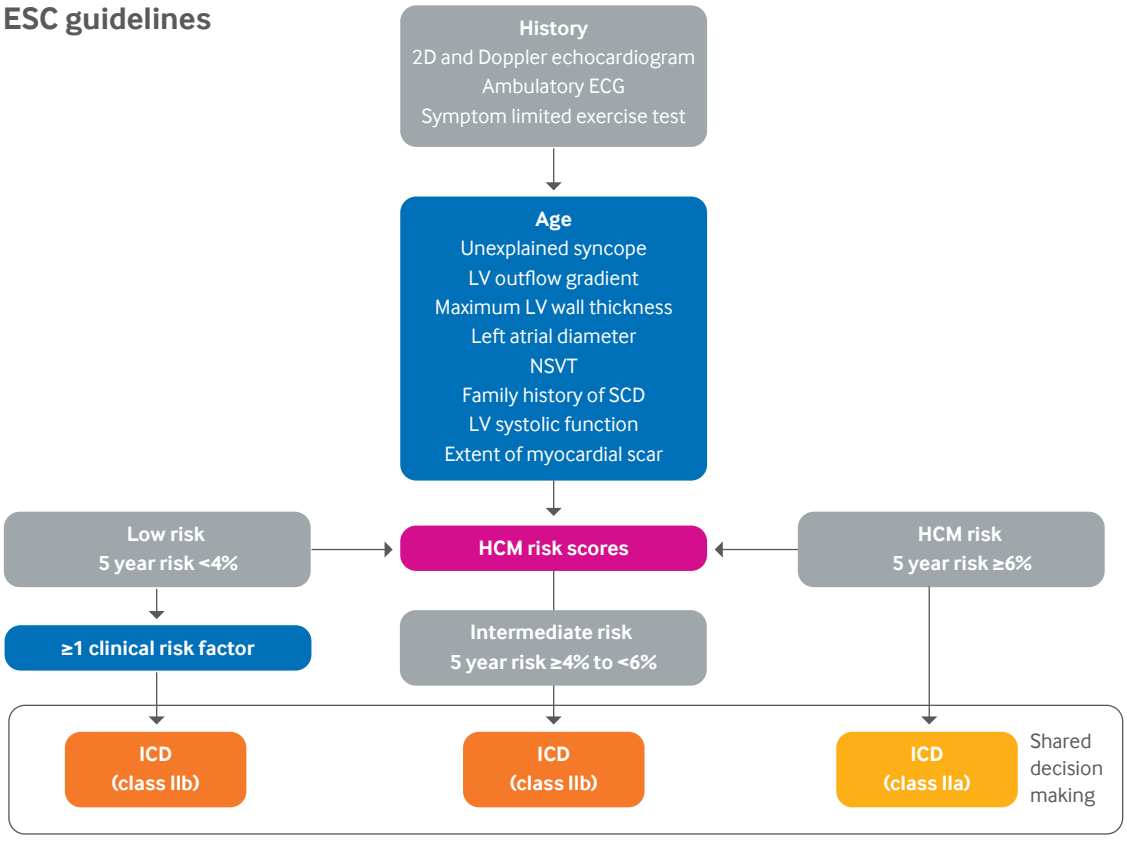


Fig 3 | Risk assessment for primary prevention of sudden cardiac death. EF=ejection fraction; ICD=implantable cardioverter-defibrillator; LA=left atrial; LV=left ventricular; LVOTO=left ventricular outflow tract obstruction; SCD=sudden cardiac death

ESC guidelines



AHA/AAC guidelines

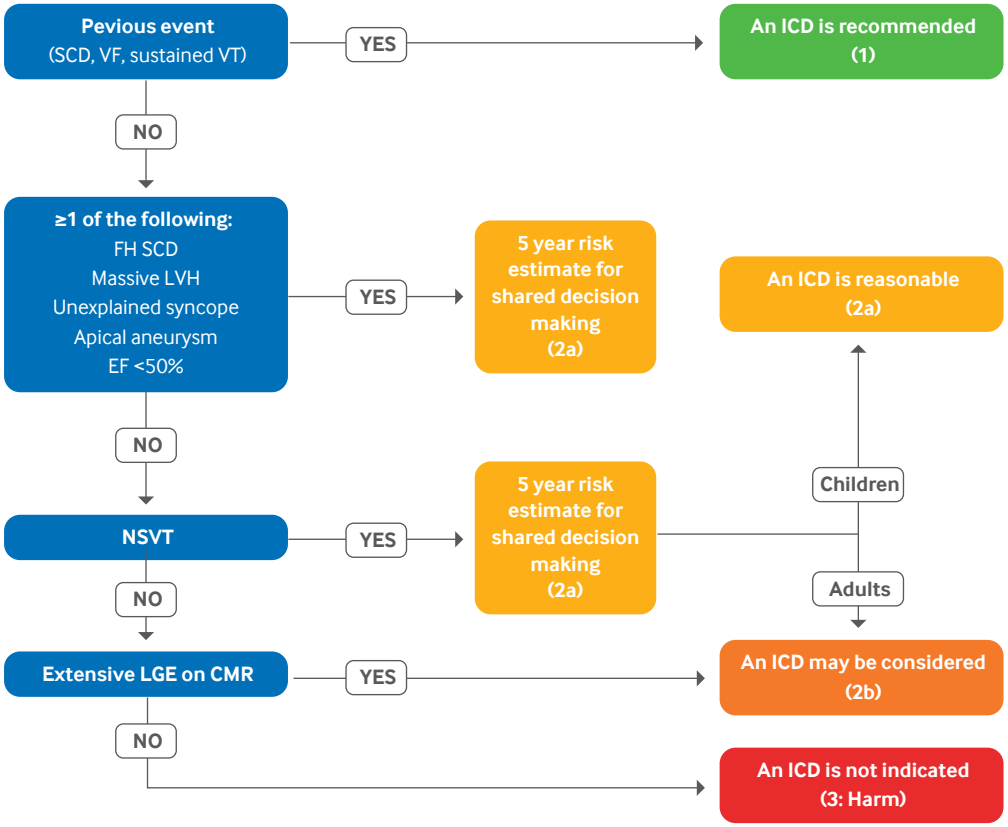


Fig 4 | Guidelines for risk assessment for primary prevention of sudden cardiac death. European Society of Cardiology (ESC) guidelines, with permission from *Eur Heart J* 2023;44:3503-626.[1] American Heart Association (AHA)/American College of Cardiology (ACC) guidelines, with permission from *Circulation* 2024;149:e1239-311.[22] CMR=cardiovascular magnetic resonance; ECG=electrocardiogram; EF=ejection fraction; FH=family history; HCM=hypertrophic cardiomyopathy; ICD=implantable cardioverter-defibrillator; LGE=late gadolinium enhancement; LV=left ventricular; NSVT=non-sustained ventricular tachycardia; SCD=sudden cardiac death; VF=ventricular fibrillation; VT=ventricular tachycardia

contemporary cardiovascular magnetic resonance defined and other risk factors, current European guidelines recommend a combined approach, using the risk score for an initial stratification, with further delineation of the need for an ICD, based on presence of other clinical factors for patients with calculator estimated low (five year <4%) risk. US guidelines suggest use of the risk calculator to define five year risk as an aid to shared decision making, which takes into account patients' values and preferences.[99 100] All guidelines recommend ICDs for patients with hypertrophic cardiomyopathy who have survived a cardiac arrest or hemodynamically significant ventricular tachycardia. Risk of sudden cardiac death is higher in children and has different risk predictors, so both guidelines recommend tailoring of risk stratification for children under 16 years old and repeated evaluations in both children and adults. Sudden cardiac death is less common in patients over 60 with hypertrophic cardiomyopathy, and individualized risk assessment is less well defined in this group.[84 101]

Specific factors that predict the risk of sudden death

Figure 3 shows specific clinical and anatomic risk factors identified to predict risk of sudden death in people with hypertrophic cardiomyopathy. Family history of sudden death in first degree relatives before age 40-50, long considered a marker of risk, has been validated in one study showing a similar rate of ICD interventions for those implanted for only this risk factor compared with those with other risk factors,[102] as well as in multivariable models of risk.[103] Personal history of non-vagal syncope is also predictive, particularly if recent. Episodes within six months are most predictive, whereas those further back than five years are not.[104]

Echocardiography will evaluate wall thickness, well described as a risk predictor, and left atrial size. LVOT obstruction has been identified as a predictor of sudden death in some but not all studies,[98 103 105] likely owing to the variability and ubiquity of resting gradient.[16-18] Whether treating LVOT obstruction decreases the risk of sudden cardiac death has not yet been determined. For these reasons, LVOT obstruction appears in the ESC calculator but not the AHA/AAC algorithm. Left ventricular dysfunction, which for patients with hypertrophic cardiomyopathy is considered to be ejection fraction <50%, is present in 8% of patients with hypertrophic cardiomyopathy and is associated with adverse outcomes, particularly in those with sarcomeric variants.[106]

Cardiac MRI has more recently been identified as providing predictive information. Extensive fibrosis (typical threshold ≥15%), detected by late gadolinium enhancement, doubles the risk of sudden cardiac death in patients with no other risk factors, with an estimated risk for life threatening arrhythmia of 6% at five years.[107] Limited data suggest that left ventricular aneurysm may be associated with a high risk of life threatening ventricular arrhythmias and transplant,[108] and it is included as a class 2a indication for an ICD in the US guidelines, although not in the European guideline. The definition of aneurysm, in differentiation from remodeling stages of apical thinning, is not well established.

Non-sustained ventricular tachycardia (NSVT) seen on 24-48 hours of ambulatory monitoring is predictive of risk of arrhythmia. Although one study showed that faster runs (>200 bpm), longer runs (>7 beats), or repetitive runs were most predictive,[109] other studies have not found these factors to differentiate risk.[110] Both US and European guidelines use duration and rate cut-offs of three beats at 120 bpm to define risk, also noting that longer and faster runs likely carry more risk. One study has found prognostic importance of NSVT detected on longer term monitoring,[111] but data are insufficient to recommend monitoring longer than 24-28 hours. NSVT carries more risk in young people,[110] and it thus carries a 2a indication for ICD in children and 2B in adults in the US guidelines. Although guidelines define thresholds for all variables, such as extent of fibrosis or length, burden, and rate of NSVT, or dichotomize, such as presence of aneurysm, risk is likely linear.

Management of atrial fibrillation

Atrial fibrillation is common in hypertrophic cardiomyopathy, being present in 5% at the time of diagnosis and developing in another 10-22% during follow-up.[112-114] Although most atrial fibrillation starts as paroxysmal, 42% of patients will go on to develop persistent atrial fibrillation. Data on association of atrial fibrillation with mortality in hypertrophic cardiomyopathy are mixed,[114 115] but patients with atrial fibrillation have more symptoms,[115] with greater functional limitation, particularly with progression to permanent atrial fibrillation.[113] As atrial fibrillation is poorly tolerated in hypertrophic cardiomyopathy, a rhythm control strategy is often preferred.[22] One small series of patients with hypertrophic cardiomyopathy undergoing atrioventricular nodal ablation for rate control showed improvement in symptoms[116]; this strategy is generally chosen for patients in whom other strategies have not been effective, and further data are needed.

Options for rhythm control, as in the general population, include drugs or catheter ablation. Anti-arrhythmic drugs, including dofetilide and

sotalol, have been found to be safe in small series of patients with hypertrophic cardiomyopathy, with effectiveness similar to published reports in the general population. Amiodarone has higher efficacy, but systemic toxicity limits its use.[117] Although disopyramide has been used to treat LVOT obstruction, its efficacy for treatment of atrial fibrillation is not reported. Class Ic agents are generally avoided in patients with structural heart disease, although no data exist specifically in patients with hypertrophic cardiomyopathy. Whether cardiac myosin inhibitors affect development and

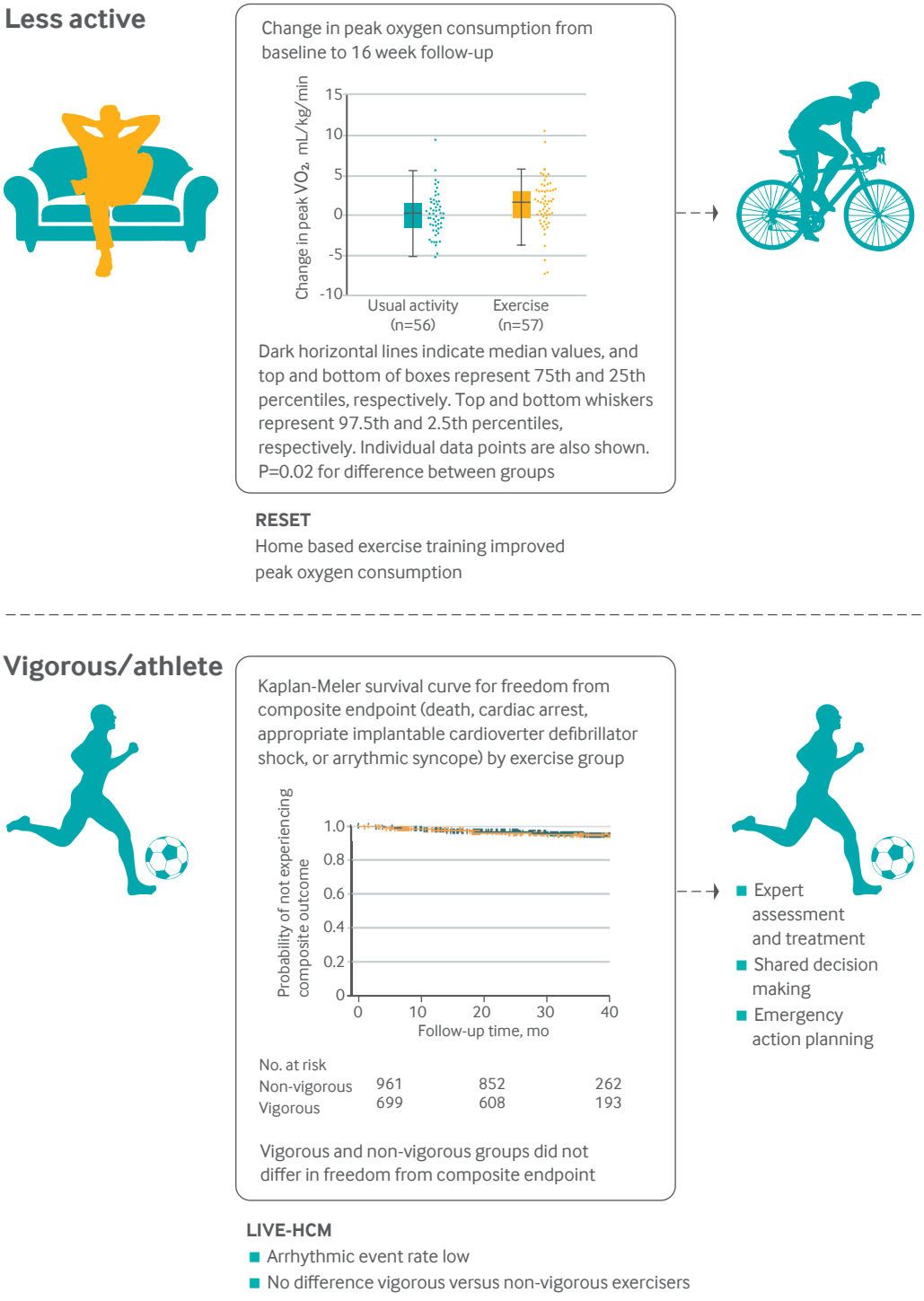


Fig 5 | Approach to exercise guidance for less active and more active individuals with hypertrophic cardiomyopathy. RESET, with permission from *JAMA* 2017;317:1349-57.[130] LIVE-HCM, with permission from *JAMA Cardiol* 2023;8:595-605[131]

progression of atrial fibrillation in hypertrophic cardiomyopathy is unknown, as described above.

Catheter ablation is another option for treatment of symptomatic atrial fibrillation. Although the overall success rate of ablation of atrial fibrillation in maintaining sinus rhythm without recurrence is lower in patients with hypertrophic cardiomyopathy than those without it (39% *v* 50% for one procedure), rates are similar for those with paroxysmal left ventricular and/or a non-dilated left atrium.[118] Most importantly, no studies have compared efficacy of anti-arrhythmic drugs versus ablation in the hypertrophic cardiomyopathy population. In the general population, randomized trials show that long term freedom from atrial fibrillation with drugs is just half that seen with ablation (risk ratio 0.54, 95% confidence interval 0.39 to 0.75).[119] Data are emerging to suggest that earlier ablation may be more effective[120]; whether this is also true in patients with hypertrophic cardiomyopathy is an important direction for future research. Current US guidelines for atrial fibrillation in hypertrophic cardiomyopathy describe either anti-arrhythmic therapy or ablation as potential first line therapies.[22] European guidelines recommend ablation after failure of an anti-arrhythmic drug but also consider ablation reasonable as a first line approach if preferred (table 2).[1]

Anticoagulation

Thromboembolic risk in atrial fibrillation is higher for patients with hypertrophic cardiomyopathy than for the general atrial fibrillation population, occurring in up to 27% of those with atrial fibrillation,[121] with a hazard ratio of 1.5 for a thromboembolic event compared with patients with atrial fibrillation without hypertrophic cardiomyopathy.[122] This risk is independent of the CHADS2-Vasc score, with many strokes seen in patients with hypertrophic cardiomyopathy with no traditional risk factors.[121] All patients with hypertrophic cardiomyopathy with clinical atrial fibrillation should thus receive anticoagulation.[22] As in the general population, direct acting oral anticoagulants (DOACs) are preferred.[122] No RCTs have compared DOACs with the vitamin K antagonist warfarin in patients with hypertrophic cardiomyopathy. In a large observational database, patients with hypertrophic cardiomyopathy treated with DOACs had similar rates of stroke or systemic embolism to those treated with warfarin and non-significantly lower rates of major bleeding.[123]

The need for anticoagulation for patients with hypertrophic cardiomyopathy with clinical atrial fibrillation is clear, but when to anticoagulate for subclinical (asymptomatic) atrial fibrillation, whether detected through external monitoring or through an implanted device (pacemaker or ICD), is less clear. Given the high risk for stroke in atrial fibrillation with hypertrophic cardiomyopathy, current US guidelines recommend extended ambulatory monitoring annually for patients with hypertrophic cardiomyopathy specific risk factors for development of atrial fibrillation as defined by the HCM-AF risk score, which includes left atrial size, age, duration of disease, and NYHA functional class.[124] The extent of atrial fibrillation that should trigger anticoagulation for patients with hypertrophic cardiomyopathy is not yet defined, which is also true for the general atrial fibrillation population. Decisions about anticoagulation should take into account the duration of episodes, atrial fibrillation burden, and clinical risk factors.[125] Development of an algorithm for benefit of anticoagulation is an important avenue of future research (as in the non-hypertrophic cardiomyopathy population).

Exercise in hypertrophic cardiomyopathy

For decades, vigorous exercise was recommended to be restricted for patients with hypertrophic cardiomyopathy, owing to concern that vigorous activity could precipitate life threatening ventricular arrhythmias.[126 127] However, the benefits of exercise, both physical and psychological, are well documented. Likely in part as a result of the extrapolation of these recommendations, patients with hypertrophic cardiomyopathy are less active than other people, with a higher prevalence of obesity, anxiety, and reduced quality of life.[128 129] Recent data in both sedentary people and competitive athletes have challenged these assumptions (fig 5).

The RESET study (Randomized Exploratory Study of Exercise Training in Hypertrophic Cardiomyopathy), hypothesized that a home based exercise program would safely improve cardiac fitness. After 16 weeks, the 67 participants randomized to the moderate intensity training showed improved exercise capacity with higher peak VO_2 compared with the usual activity group (n=69), with a between group difference of 1.27 (95% confidence interval 0.17 to 2.37; P=0.02), as well as subjective improvement, with no arrhythmic events.[130] On the basis of this study, the AHA/ACC guidelines now include mild-moderate intensity recreational exercise as a class I recommendation.[22] More recent studies of high intensity training have shown similar findings (table 2).[132 133]

Athletes

For athletes with a diagnosis of hypertrophic cardiomyopathy, data suggesting that risks of continuing sports may be lower than previously hypothesized are mounting. Several retrospective series of athletes who have continued to participate in sports after a diagnosis of hypertrophic cardiomyopathy have not shown a high risk of arrhythmic events in those who have undergone expert assessment and treatment.[134-136] The prospective observational LIVE-HCM study followed 1660 individuals with hypertrophic cardiomyopathy for three years, finding that those exercising more vigorously (participating in at least one activity of ≥6 METs (metabolic equivalents) for ≥60 hours per year,[137] close to half of these competitively), did not have a higher rate of arrhythmic outcomes

including death, cardiac arrest, appropriate ICD shock, or arrhythmic syncope.[131] Hypertrophic cardiomyopathy carries a risk of ventricular arrhythmias and sudden cardiac death, but in this study this endpoint was not increased with exercise, occurring in 4.7% of the vigorous and 4.6% of the non-vigorous exercisers (adjusted hazard ratio 1.01, upper 95% one sided confidence interval 1.48, below the pre-specified non-inferiority bound). On the basis of these studies, current US recommendations advise consultation with an expert for risk assessment and shared decision making for athletes with hypertrophic cardiomyopathy wishing to continue competition.[22 138] ESC guidelines similarly recommend an individualized approach to return to sport for athletes with a diagnosis of hypertrophic cardiomyopathy, rather than the blanket restrictions of the past (table 2).

Management of advanced heart failure in hypertrophic cardiomyopathy

Although substantial improvements have been made in the medical and surgical management of patients with hypertrophic cardiomyopathy, a smaller subset of patients (7-10%)[139] progress to experience advanced heart failure symptoms characterized by severe functional limitation and refractory heart failure symptoms in the absence of LVOT obstruction.[140] Recognition of advanced heart failure in hypertrophic cardiomyopathy remains challenging, as many overlapping clinical phenotypes exist in this subset of patients. Notably, a significant reduction in left ventricular ejection fraction (LVEF) to <50% by imaging, which is classically associated with other forms of advanced cardiomyopathy, may not always be present or as severe in patients with hypertrophic cardiomyopathy developing heart failure. Only 30% of patients with hypertrophic cardiomyopathy with heart failure will have an LVEF <50% at presentation, with most patients having normal LVEF with restrictive physiology.[140] Left ventricular dysfunction is uncommon, developing in 7.5% over 15 years, but once this occurs 35% progress to death, transplant, or mechanical assist device over median of 8.4 years, as shown in a cohort of more than 6500 patients in the SHARE registry [106]

Although RCTs of conventional guideline directed neurohormonal therapy for systolic heart failure in hypertrophic cardiomyopathy remain lacking, these therapies are still recommended as tolerated.[22 141 142] More often, a combination of mild systolic dysfunction and significant restrictive physiology with diastolic dysfunction with subsequent pulmonary hypertension drives functional decline in these patients.[143] As such, a comprehensive assessment with a combination of imaging, cardiopulmonary exercise testing, and invasive hemodynamic assessment is often necessary for diagnosis and timely consideration for advanced heart failure therapies.[144]

Given the noted challenges of using imaging alone to classify the severity of heart failure in hypertrophic cardiomyopathy, cardiopulmonary exercise testing (CPET) is an essential non-invasive tool to assess cardiopulmonary and skeletal muscle limitations during exercise. Specifically, CPET parameters such as peak oxygen consumption (pVO_2), ventilatory efficiency (VE/VCO_2 slope), and anaerobic threshold can be useful for prognosis independent of LVEF and guide the need for advanced heart failure therapies such as cardiac transplantation.[145] Importantly, although pVO_2 and VE/VCO_2 slope thresholds (pVO_2 <14 off β blocker, pVO_2 <12 on β blocker, VE/VCO_2 slope >35) can be used as a guide for consideration for transplantation, these are validated in patients with advanced systolic heart failure and are not clearly delineated for hypertrophic cardiomyopathy specifically.[146] As many patients with advanced heart failure with hypertrophic cardiomyopathy are younger, age stratified percentage predicted pVO_2 of <50% is as important as absolute values when using this modality for prognostication.

With progressive remodeling in hypertrophic cardiomyopathy, a combination of both systolic and diastolic dysfunction can occur and invasive hemodynamic assessment with right heart catheterization becomes an important tool for assessment and prognostication. Detection of elevated left sided filling pressures, development of post-capillary pulmonary hypertension, and decreased cardiac output and index are all associated with more advanced disease. Development of pulmonary hypertension specifically can be insidious and a marker of end organ involvement with progressive cardiomyopathy. As irreversible pulmonary hypertension can be a contraindication for transplantation given a risk of postoperative right ventricular dysfunction, invasive assessment remains a critical tool for early detection in patients with a significant symptom burden and higher risk non-invasive parameters via imaging or CPET testing.[147]

Once advanced disease progression associated with functional limitation is identified with imaging, exercise testing, and invasive hemodynamic assessment, cardiac transplantation remains the most definitive surgical solution for advanced heart failure in hypertrophic cardiomyopathy. Figure 6 shows evaluation for transplantation and its indications in the US and UK. In addition to identifying prognostic factors for heart failure, ensuring that all medical, interventional, and surgical options for obstructive physiology are thoroughly considered is similarly important. Randomized data are lacking, but small series suggest that cardiac resynchronization may improve exercise capacity and/or NYHA class for patients meeting criteria for ICD and cardiac resynchronization therapy.[148] US guidelines modify standard ejection fraction criteria for cardiac resynchronization therapy to <50%,[22] although European guidelines do not (table 2).[1]

Survival outcomes after transplantation in hypertrophic cardiomyopathy remain similar to those for other forms of advanced heart failure, with one

CPET guidance metrics
- pVO_2 <14 or pVO_2 <12 on β blocker
- Age stratified percentage predicted pVO_2 <50%
- VE/VCO_2 slope >35

Right heart catheterization guidance parameters
- PCWP >20 mm Hg
- PVR ≥2.5 Woods units
- TPG ≥15 mm Hg
- CI ≤2.2 L/min/m^2

UK: NHS

No specific criteria for HCM

Super urgent heart allocation
- VA-ECMO
- Imminent risk of dying, not suitable for long term VAD

Urgent heart allocation

Category 21: dependent on inotropes and/or IABP

Category 23: high risk of dying or irreversible complication

Routine heart allocation
- Persistent NYHA III/IV
- pVO_2 <14 or <50% predicted on CPET
- CI <2
- Deteriorating WHO group II pulmonary hypertension
- Recurrent ventricular arrhythmia
- Deteriorating liver function due to right heart failure

US: UNOS

Specific criteria for HCM

Status 1

VA-ECMO, BiVAD, MCSD with life threatening arrhythmias

Status 2

Continuous monitoring of hemodynamic data (all of following)

a) Maximally tolerated inotropic dosages

b) Either of the following on maximally tolerated inotropes:

a) ≥2 indicators hemodynamic instability

b) One indicator hemodynamic instability and ≥1 indicator end organ dysfunction

Hemodynamic instability indicators:
- SBP <90 mmHg
- LAP/RAP, LVEDP/RVEDP, PCWP >20 mm Hg
- CI ≤2.2 L/min/m^2
- $Sv0_2$ <50%
- TPG ≥15 m mHg
- (PVR) ≥ 2.5 Wood units

End organ dysfunction indicators:
- Arterial lactate to 2.5 mmol/L
- Serum creatinine >50% above baseline
- Total bilirubin >50% above baseline
- AST or ALT >2x upper limit of normal

Status 3

Admitted to hospital with NYHA IV symptoms with all of the following:

1. Has one :
   - Invasive pulmonary artery catheter
   - Daily hemodynamic monitoring of cardiac output and left ventricular filling pressures
2. Continuous inotropic infusion to improve end organ perfusion/function
3. Before inotropes, ≥2 of:
   - SBP <90 mm Hg
   - LAP/RAP, LVEDP/RVEDP, PCWP >20 mm Hg
   - TPG ≥15 mm Hg
   - PVR ≥2.5 Woods units
   - CI <1.8 L/min/m^2

Status 4:
- Canadian Cardiovascular Society Grade IV angina pectoris
- (NYHA) class IIII/V symptoms with either:
- CI <2.2 L/min/m^2
- LAP/RAP, LVEDP/RVEDP, PCWP >20 mm Hg
- VT, VF, SCD

Fig 6 | Transplant evaluation: US and UK. ALT=alanine aminotransferase; AST=aspartate aminotransferase; BiVAD=biventricular assist device; CPET=cardiopulmonary exercise testing; HCM=hypertrophic cardiomyopathy; IABP=intra-aortic balloon pump; LAP=left atrial pressure; LVEDP=left ventricular end diastolic pressure; MCSD=mechanical circulatory support device; NYHA=New York Heart Association; PCWP=pulmonary capillary wedge pressure; PVR=peripheral vascular resistance; RAP=right atrial pressure; RVEDP=right ventricular end diastolic pressure; SBP=systolic blood pressure; SCD=sudden cardiac death; TPG=transpulmonary pressure gradient; VAD=ventricular assist device; VA-ECMO=venoarterial extracorporeal membrane oxygenation; VF=ventricular fibrillation; VT=ventricular tachycardia

year survival of approximately 91%.[144] Recognition of unique factors related to progressive restrictive physiology in advanced heart failure in hypertrophic cardiomyopathy has led to amendments in the transplant allocation system in the US, which has improved waitlist mortality and transplantation rates for patients with hypertrophic cardiomyopathy.[149] Furthermore, mechanisms to expand the donor pool with donation after circulatory death and hepatitis C nucleic acid positive donors have in parallel improved access to suitable donors for all patients awaiting transplantation.

Mechanical circulatory support (MCS) options, either temporary before transplant or durable in the form of left ventricular assist devices (LVADs), can be feasible in patients with hypertrophic cardiomyopathy but overall require a nuanced approach given anatomic constraints for specific intracardiac devices. Specifically with LVAD therapy, small left ventricular dimensions can increase the probability of inflow cannula suction increasing the chances of device suction and arrhythmia. LVAD implantation has been attempted in select cases of hypertrophic cardiomyopathy but primarily in patients with more significant left ventricular dysfunction and dilation (>5.0 cm).[150] Temporary MCS poses similar anatomic challenges with either microaxial transvalvular flow pumps or extracorporeal LVAD. Venoarterial extracorporeal membrane oxygenation remains a final option for refractory circulatory shock as a bridge to surgical heart failure therapies.

Emerging treatments

Non-obstructive disease

Subanalyses of the CMI trials have shown that, in addition to reduction in LVOT gradient, CMIs affect cardiac structural parameters and diastolic function. An exploratory substudy from VALOR data suggests that mavacamten improves echocardiographic parameters of diastolic dysfunction.[151] Similarly, data from SEQUOIA-HCM show that patients taking aficamten had improvements in echocardiographic diastolic parameters compared with placebo.[152]

On the basis of these findings, CMIs are under investigation in patients with non-obstructive hypertrophic cardiomyopathy. Two phase 3 RCTs are ongoing: ACACIA-HCM (Trial to Evaluate The Efficacy and Safety of Aficamten Compared to Placebo in Adults with Symptomatic nHCM) and ODYSSEY-HCM (A Study of Mavacamten in Non-Obstructive Hypertrophic Cardiomyopathy).[153 154] Bristol Myers Squibb provided an update on the ODYSSEY-HCM trial on 14 April 2025,[155] showing no significant difference in the primary outcomes compared with placebo; however, the results have not been peer reviewed or published elsewhere.

Sodium-glucose cotransporter (SGLT) inhibitors, which are established as beneficial in patients with heart failure with both reduced and preserved ejection fraction, may also have potential benefit in non-obstructive hypertrophic cardiomyopathy.[156] Early, non-randomized data suggest that SGLT-1/2 inhibitors may reduce cardiovascular events in patients with hypertrophic cardiomyopathy, and a randomized, placebo controlled, multinational phase 3 clinical trial is under way.[157 158]

Targeted genetic therapies

The use of gene replacement (or enhancement) therapy to restore protein levels in settings where they are absent, reduced, or non-functional as the result of loss of function variants is under investigation. Pre-clinical studies in experimental murine models have shown that a single administration of adeno-associated virus 9 (AAV9)-*MYBPC3* successfully prevented the development of cardiac hypertrophy and dysfunction,[159] as well as myocardial disarray and fibrosis. On the basis of these pre-clinical studies, *MYBPC3* is the target of the first clinical trial of gene replacement therapy for sarcomeric hypertrophic cardiomyopathy. MyPeak-1 is an open label phase 1b study (NCT05836259) in which recombinant AAV9-*MYBPC3* (TN-201) is being administered to adults with symptomatic, non-obstructive hypertrophic cardiomyopathy caused by truncating variants in *MYBPC3*.[160] This study began enrolling in late 2023 and plans to enroll a total of six patients in low and high dose cohorts.

Gene editing is also being explored as a potential therapy to preemptively treat hypertrophic cardiomyopathy in carriers of sarcomeric variants. Missense variants in *MYH7* and other sarcomere genes are believed to cause hypertrophic cardiomyopathy mostly through gain of function mechanisms. In experimental models, use of adeno-associated viruses for delivery of gene editing materials has shown beneficial effects as a proof of concept, with prevention of the development of the functional, histopathological, and molecular phenotypes of hypertrophic cardiomyopathy including prevention of hypertrophy.[161 162] However, dose dependent editing of the wild type allele can lead to reduced contractile function.[162]

Overall, although these initial results with gene enhancement and targeted base editing are promising, whether, or to what extent, the therapies can reverse the hypertrophic cardiomyopathy phenotype in patients with established disease remains to be seen, particularly for those who have already developed significant scar burden. The cohort tested represents another challenge—many years will be needed to determine whether genetic therapies can prevent phenotypic expression in younger unaffected carriers, particularly given the known variable penetrance. Moreover, the genetic heterogeneity of hypertrophic cardiomyopathy poses significant challenges for genetic therapies, as multiple versions of the therapies will likely need to be developed to cover the large number of contributing genes.[163] Gene therapeutics for hypertrophic cardiomyopathy is in early phase trials, with the most significant limitation being cardiac directed delivery. Current adeno-associated virus

vectors transduce the heart but need high titers that necessitate aggressive immunosuppressive regimens to reduce the risk of systemic toxicity. Identification of novel vectors is an important avenue of ongoing research.

Emerging risk assessment modalities

Molecular imaging may provide novel predictive information on sudden death risk. ^{123}I-metaiodobenyzlguanidine is a single photon emission computed tomography radiotracer that characterizes sympathetic innervation to the heart. In hypertrophic cardiomyopathy, abnormalities of cardiac innervation reflected by abnormal ^{123}I-metaiodobenzylguanidine have shown associations with ventricular arrhythmias,[164] as well as with progression of myocardial damage.[165] Another area in which molecular imaging may provide additional value for risk stratification of hypertrophic cardiomyopathy is in the characterization of myocardial fibrosis. Radiotracers based on fibroblast activation protein inhibitor (for example, ^{18}F-FAPI) measure levels of fibroblast activation in the myocardium, reflecting an active fibrotic process, which has correlated with myocardial function,[166] as well as with sudden cardiac death.[167]

Guidelines

Table 2 summarizes recommendations from the ESC and AHA/ACC on the diagnosis and management of hypertrophic cardiomyopathy.[1 22]

Conclusion

Hypertrophic cardiomyopathy is a common genetic cardiomyopathy with a global presence that remains underdiagnosed and undertreated. Although first line medical and surgical therapy has been largely unchanged over the past half century, recent developments on multiple fronts have led to more treatment options and improved quality of life for patients. CMI therapy has changed the treatment paradigm for obstructive hypertrophic cardiomyopathy. Emerging treatments, including targeted gene therapy, have the potential to be disease modifying. Our understanding of the management of arrhythmias, risk of sudden cardiac death, and recommendations for exercise has evolved. For patients with advanced disease, advances in MCS and cardiac transplantation offer an opportunity for improved survival in an increasing number of patients. Given the increased complexity of managing hypertrophic cardiomyopathy, multidisciplinary teams, including

GLOSSARY OF ABBREVIATIONS

- ACC—American College of Cardiology
- AHA—American Heart Association
- ASA—alcohol septal ablation
- CCB—calcium channel blocker
- CMI—cardiac myosin inhibitor
- CPET—cardiopulmonary exercise testing
- DOAC—direct acting oral anticoagulant
- ESC—European Society of Cardiology
- ICD—implantable cardioverter-defibrillator
- LVAD—left ventricular assist device
- LVEF—left ventricular ejection fraction
- LVOT—left ventricular outflow tract
- MCS—mechanical circulatory support
- MRI—magnetic resonance imaging
- NSVT—non-sustained ventricular tachycardia
- NYHA—New York Heart Association
- RCT—randomized controlled trial
- REMS—Risk Evaluation and Mitigation Strategy
- SRT—septal reduction therapy
- VA-ECMO—venoarterial extracorporeal membrane oxygenation

QUESTIONS FOR FUTURE RESEARCH

- How can timing, expanding populations, and concomitant therapies be optimized in the use of cardiac myosin inhibitors?
- Can gene modifying therapies alter the course of disease, and what is the optimum timing?
- Can better predictors of sudden death, including use of wearable devices, be identified?
- What is the extent of atrial fibrillation that warrants anticoagulation?
- What is the impact of exercise on the course of disease?

PATIENT INVOLVEMENT

We shared a draft of the manuscript with four patients who are living with hypertrophic cardiomyopathy. Their thoughtful review and feedback allowed us to make improvements to the final document. Specific themes that emerged from their commentary, and have been incorporated into the manuscript text and research questions, included:

- Implications of long term use of cardiac myosin inhibitors and their potential for cardiac remodeling, as well as the need for research in this area
- Questions surrounding the emergence of gene therapy, including safety concerns and the potential for disease modification
- The need for a more personalized and comprehensive approach to risk assessment for sudden cardiac death
- Concern that clinicians emphasize limitation of physical activity despite newer data, and emphasis that clinicians should assess specific exercise goals in patients and individualize recommendations
- Challenges with management of atrial fibrillation, including complex decisions about initiation and maintenance of anticoagulation, and the need for more investigation in this area
- Emphasis on early identification of patients at risk for progression to advanced heart failure and the need to consider these patients as distinct from other groups more frequently managed with mechanical circulatory support and heart transplantation

attention to psychological support, should be used to deliver the highest level of patient care.

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