




EJHF expert consensus statement on the diagnosis and management of hypertrophic cardiomyopathy

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Abstract

Hypertrophic cardiomyopathy (HCM) is the most prevalent genetic cardiac disease and a leading cause of heart failure, arrhythmia, and sudden cardiac death in both young and older adults. This consensus document was developed by a multidisciplinary panel of European and U.S. experts in HCM, imaging, electrophysiology, genetics, and heart failure. While it aligns with the 2023 ESC and 2024 AHA/ACC guidelines on HCM, the paper addresses areas where clinicians might require further guidance. Key sections include phenotypic classification, diagnostic strategies incorporating multimodal imaging and genetic testing, and risk stratification for sudden cardiac death. The document outlines therapeutic pathways for pharmacologic treatment, including beta-blockers, calcium channel blockers, disopyramide, and cardiac myosin inhibitors such as mavacamten and aficamten, as well as indications for septal reduction therapies. Management of atrial fibrillation, hypertension, coronary artery disease, pregnancy, paediatric HCM, and comorbidities is discussed in detail. Importantly, the consensus addresses current controversies including optimal risk stratification models, the care of genotype-positive/phenotype-negative individuals, and exercise recommendations. Finally, the manuscript highlights future directions such as gene therapy, precision medicine approaches, use of artificial intelligence and novel biomarkers for screening and diagnosis.

Keywords

Hypertrophic cardiomyopathy • Obstructive HCM • Non-obstructive HCM • Myosin inhibitors • Septal reduction therapy • Consensus recommendations

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Introduction

Hypertrophic cardiomyopathy (HCM) is the most common monogenic cardiovascular disorder and affects ~1 in 500 individuals globally.¹ It is characterized by unexplained left ventricular hypertrophy (LVH), with up to 30%–50% showing pathogenic variants in genes encoding sarcomeric proteins. HCM exhibits a broad phenotypic spectrum, ranging from asymptomatic individuals to those experiencing heart failure, atrial or ventricular arrhythmias, or sudden cardiac death (SCD).^{2,3} Historically, therapeutic approaches in HCM have focused on alleviating symptoms and preventing disease-related complications, including SCD.^{4,5} While conventional therapy for obstructive forms (oHCM) has included beta-blockers (BBs), calcium channel blockers (CCBs), and septal reduction therapies (SRTs), the emergence of cardiac myosin inhibitors (CMIs) has introduced a targeted therapeutic modality aimed at modulating sarcomere function.^{6–8} Non-obstructive HCM (nHCM), previously considered to have a milder clinical course is now recognized to be associated with a substantial burden of heart failure and arrhythmias, particularly in older individuals and those with comorbidities.^{9,10}

In light of recent major advances, including the publication of the 2023 ESC Guidelines on Cardiomyopathies and the 2024 AHA/ACC HCM Guidelines, as well as pivotal clinical trials on novel pharmacologic agents, this expert consensus statement provides a multidisciplinary, evidence-based framework for the diagnosis and management of HCM.^{6,11} The document reflects consensus among experts in cardiomyopathy, imaging, electrophysiology, genetics, and heart failure and highlights both established recommendations and areas of ongoing debate or insufficient evidence. This consensus statement was developed and agreed upon during a dedicated international expert meeting, bringing together specialists from Europe and the United States.

Classification of HCM

HCM is broadly classified based on the presence or absence of dynamic left ventricular outflow tract (LVOT) obstruction. oHCM is defined by a resting or provoked LVOT gradient ≥ 30 mmHg, typically resulting from basal septal hypertrophy and systolic anterior motion (SAM) of the mitral valve apparatus.^{4,6} nHCM is characterized by the absence of significant dynamic LVOT obstruction at rest or with physiological provocation. In this phenotype, symptoms are frequently driven by diastolic dysfunction, impaired myocardial relaxation, microvascular ischaemia, and atrial arrhythmias.¹²

Although both forms may share overlapping genetic variants and morphological features, they differ substantially in their haemodynamic behavior, therapeutic implications and outcomes.¹³ Importantly, these phenotypes lie on a continuum rather than representing distinct disease entities. Some patients may develop obstruction over time as hypertrophy progresses or haemodynamic boundaries including contractility change.^{4,14} The ratio of patients with oHCM:nHCM is debated and existing evidence ranges from 1:1 to 2:1.¹⁵ This might be due to inconsistent assessment of provocation manoeuvres and phenotyping heterogeneities.

HCM also encompasses rarer sub-phenotypes such as apical HCM, mid-ventricular obstruction, and HCM with dominant restrictive features. Distinguishing HCM from phenocopies (e.g. cardiac amyloidosis, Anderson-Fabry disease, Noonan syndrome etc.) becomes imperative with an increasing number of specific treatments for these conditions. Diagnostic clues include red flags such as relative low voltage on electrocardiogram (ECG), extracardiac features, or atypical age of onset to name only three.^{16,17}

Diagnostic evaluation of HCM

A thorough diagnostic work-up of suspected HCM requires integration of clinical findings, multimodal imaging, family history, and genetic

testing.⁶ Echocardiography is broadly available and remains the first-line modality. Left ventricular (LV) wall thickness ≥ 15 mm in the absence of other causes (e.g. hypertension, valve disease) is the main diagnostic imaging criterion in adults.^{6,11} In children and adolescents, HCM should be diagnosed based on age-, sex-, and body surface area (BSA)-adjusted Z-scores, with a threshold of LV wall thickness typically exceeding +2 standard deviations above the mean.¹⁸ However, recent evidence suggests that sex-specific and body size-adjusted thresholds may improve diagnostic accuracy, as myocardial wall thickness varies by sex, age, and BSA and women tend to present with less wall thickness.^{18–20} These refined criteria may help avoid underdiagnosis in women and overdiagnosis in tall or athletic individuals.

Repeated assessment is critical in evaluation of latent obstruction.⁶ The Valsalva manoeuvre remains an invaluable tool for detecting latent LVOT obstruction. When feasible, a standardized, goal-directed Valsalva, defined as sustained intrathoracic pressure of 40 mmHg for 10 s using a calibrated manometer or mouthpiece device, should be employed to enhance reproducibility and diagnostic yield.^{21,22} However, its sensitivity and applicability across diverse patient populations remain under investigation, and self-directed Valsalva remains a reasonable alternative in routine practice. In patients with exertional or meal-related symptoms but inconspicuous resting gradients, post-prandial echocardiography may be useful to provoke obstruction and clarify symptom correlation.²³ Physiologic stress testing using upright treadmill and semi-supine bicycle echocardiography are commonly used to provoke LVOT gradients, each with distinct advantages and limitations. In clinical practice, the choice should be guided by the primary diagnostic goal. Treadmill testing better replicates daily exertion, allows assessment of exercise capacity, blood pressure response, and arrhythmia detection, and provides robust sympathetic stimulation that reliably induces gradients, though imaging is restricted to the recovery phase.^{24,25} In contrast, semi-supine bicycle testing enables continuous imaging during exercise, allowing detailed evaluation of obstruction onset, mitral regurgitation, and pulmonary pressures. It has been reported that treadmill testing reveals LVOT obstruction in a higher number of patients compared with semi-supine bicycle testing, possibly due to more pronounced physiological stress.²⁵ Thus, the choice of modality should be individualized according to the clinical scenario, diagnostic priorities, and local expertise.

Late gadolinium enhancement (LGE) quantification is an essential component of risk stratification in HCM, with fibrosis burden ($>15\%$) increasingly recognized as a clinically relevant threshold for implantable cardioverter-defibrillator (ICD) consideration.²⁶ However, variability in acquisition and post-processing techniques, including thresholding methods and scanner differences, limits the universal application of a fixed cut-off. LGE should be interpreted in conjunction with existing scoring systems (ESC risk score) or additional risk markers such as non-sustained ventricular tachycardia (NSVT) or genotype.²⁷ Native T1 mapping and extracellular volume (ECV) further support the diagnostic evaluation, particularly in identifying phenocopies such as Fabry disease or cardiac amyloidosis.²⁸ While their prognostic role remains to be defined, these parameters improve diagnostic accuracy and should be routinely included in cardiac magnetic resonance imaging (CMR) protocols for suspected cardiomyopathy. Prospective data are awaited to clarify their role in clinical decision-making.²⁹

Family screening with ECG and echocardiography is advised in first-degree relatives.⁶ Genetic testing should be considered in patients with confirmed HCM, particularly in the context of familial disease, early onset, or atypical/syndromic features.⁶ Sarcomeric gene mutations, most commonly in *MYH7*, *MYBPC3*, and *TNNI2*, are identified in a substantial proportion of cases.^{2,30} Broad gene-panels with inclusion of phenocopy genes is recommended by the author group. Studies show large heterogeneity of e.g. prevalence of *TTR* variants (amyloidosis) ranging from 1.5% to 20% of 'HCM' patients.^{31–34} While we raise questions related to phenotyping accuracy in some studies, it still remains important for

those individuals that otherwise would be withheld prognosis improving therapeutic options, such as treatment of ATTR amyloidosis. Integrating genetic information, particularly the presence of sarcomeric pathogenic variants, may enhance SCD risk stratification and serve as a valuable adjunct for certain variants in borderline cases when considering ICD implantation.³⁵

Ambulatory ECG monitoring is essential for detecting arrhythmias in HCM, particularly AF and NSVT, both of which are relevant for stroke prevention and SCD risk stratification.²⁵ In asymptomatic patients without known arrhythmias, annual 24-h Holter monitoring remains a reasonable standard. However, more frequent (e.g. every 6–12 months) or extended monitoring may be appropriate in higher-risk individuals, particularly those with intermediate SCD risk, palpitations, unexplained syncope, or marked left atrial enlargement.^{4,36} While traditional Holter monitors are widely used, longer-duration recordings or wearable technologies may improve detection in selected patients, although their specificity and clinical impact require further validation.³⁷

In patients with HCM, evaluation for concomitant coronary artery disease (CAD) should follow standard recommendations based on cardiovascular risk factors, age, and symptom profile.^{6,18,38} In individuals presenting with angina, angina-equivalent dyspnoea, or other exertional symptoms, coronary assessment should be considered. Non-invasive coronary CTCA is often preferred in patients with low-to-intermediate pretest probability to exclude epicardial CAD and assess for myocardial bridging, which is more prevalent in HCM and may contribute to ischaemia symptoms.³⁹ Functional stress imaging may also be used, but perfusion abnormalities should be interpreted with caution, as they may reflect microvascular dysfunction or dynamic LVOT obstruction rather than epicardial disease.^{40,41} Invasive coronary angiography offers the advantage of haemodynamic assessment, including the Brockenbrough–Braunwald–Morrow sign, which may help unmask dynamic LVOT obstruction in symptomatic patients with borderline or non-significant gradients on echocardiography.⁴² In selected cases, such as prior to alcohol septal ablation (ASA) or surgical myectomy, anatomical coronary imaging is essential for procedural planning. As in the general population, comprehensive cardiovascular risk assessment and primary prevention strategies remain essential.³⁸

Transesophageal echocardiography (TEE) is useful in patients with oHCM and suspected anatomical contributors to SAM, such as subvalvular membranes, anomalous chordae, or papillary muscle malposition.⁴³ It should be considered in non-responders to therapy or when interventions like myectomy, are planned. In such cases, TEE aids in defining mitral and subvalvular anatomy.

Pharmacologic treatment of HCM

Medical therapy remains the cornerstone for symptom control in HCM. Treatment strategies are tailored based on the presence or absence of LVOT obstruction, symptom severity, heart rate, blood pressure, and comorbidities. The primary goals include alleviating symptoms, improving functional capacity, and reducing the risk of arrhythmic complications and the need to integrate conventional myectomy with mitral valve repair.⁴⁴

Beta-blockers

Beta-blockers are currently first-line therapy in symptomatic patients with HCM, particularly in the presence of LVOT obstruction.⁶ Their negative chronotropic and mild negative inotropic effects help reduce LVOT gradients, improve diastolic filling, and alleviate exertional symptoms such as dyspnoea and chest discomfort.⁴⁵ β_1 -selective BB, such as metoprolol succinate and bisoprolol, are recommended.^{45,46} Other agents, such as atenolol, are less preferred due to a shorter half-life and limited supporting data. Carvedilol or Nebivolol owing to its vasodilating α_1 -blocking effect, is generally not recommended in oHCM, as it may worsen dynamic

obstruction.⁴⁷ While metoprolol remains the most widely used beta-blocker, supported by clinical experience and inclusion in major trials, bisoprolol may offer theoretical advantages due to its greater β_1 -selectivity and more stable 24-h heart rate control.⁴⁸ In patients with HCM receiving beta-blocker, a resting heart rate between 50 and 70 bpm is generally appropriate, balancing gradient reduction with the issues connected to bradycardia. Dose adjustment should be considered if resting heart rate falls below 40 bpm or if bradycardia-related symptoms occur. Individual factors, including age, activity level, and Holter or exercise-derived heart rate profiles, should inform therapeutic decisions, with the overall aim of optimizing symptom relief and haemodynamic response. New light on the primary use of beta-blocker is shed by results of the MAPLE-HCM trial, comparing Metoprolol against aficamten.⁴⁹

Calcium channel blockers

In patients who are intolerant of beta-blocker, non-dihydropyridine CCBs such as verapamil and diltiazem are considered effective alternatives for symptom relief in HCM, particularly in the setting of obstruction.^{6,18} These agents exert negative chronotropic and inotropic effects, helping to improve diastolic filling, reduce myocardial oxygen demand, and control exercise-induced symptoms.^{50,51} Verapamil is more extensively studied and may be preferred in clinical practice; however, no head-to-head trials exist, and both agents are considered acceptable options.⁵² Importantly, verapamil should be used with caution. In the presence of markedly elevated LVOT gradients, severe pulmonary hypertension, or baseline systemic hypotension, it can precipitate haemodynamic instability due to its vasodilatory and negative inotropic properties.^{53–55} Recent reports have described cases of cardiogenic shock and conduction disturbances related to verapamil toxicity in oHCM.⁵⁴ Moreover, haemodynamic studies in patients with pulmonary hypertension showed that, while verapamil reduced pulmonary vascular resistance, it also exerted profound depressant effects on right ventricular performance, occasionally resulting in hypotension and even cardiac arrest.^{55,56} Anecdotally, CCBs may improve angina, particularly in non-obstructive HCM, though data on antihypertrophic or disease-modifying effects are limited and of uncertain clinical significance.⁵⁷ In real-world studies, many HCM patients receive vasodilating CCBs, either for control of arterial hypertension or insufficient knowledge on their potential worsening effect on LVOT obstruction.

Disopyramide

Disopyramide, a class Ia antiarrhythmic with potent negative inotropic effects, may be added in patients with persistent obstruction and symptoms despite beta-blockade or CCB.⁶ While it can reduce LVOT gradients and improve symptoms, its use is limited by anticholinergic side effects, QT prolongation, and restricted availability in many countries. ECG monitoring, particularly of QTc interval, is essential during dose titration, and renal function should be monitored, especially in older patients.⁵⁸ Given the emergence of newer agents such as myosin inhibitors, disopyramide may play a minor role in future treatment algorithms, but may remain a reasonable option when other therapies are unavailable or contraindicated.

Cardiac myosin inhibitors

The development of CMIs has introduced a disease-specific treatment approach for HCM by targeting sarcomeric hypercontractility. These agents directly reduce actin-myosin cross-bridge formation, thereby decreasing contractile force, sarcomere stiffness and LVOT obstruction.⁷ Mavacamten, the first-in-class CMI, has demonstrated substantial benefit in patients with symptomatic oHCM, including significant reductions in LVOT gradients, improvements in New York Heart Association (NYHA) class, exercise capacity, and quality of life.^{7,59} Favourable cardiac remodelling, including reductions in LV mass, E/E', and myocardial

strain, has also been observed in longer-term studies.^{60,61} Treatment requires echocardiographic monitoring of LVEF due to the risk of reversible systolic dysfunction, particularly at higher doses. Drug–drug interactions, especially with CYP2C19 and CYP3A4 substrates or inhibitors, must be carefully considered.⁷ Aficamten, a next-in-class CMI with a shorter half-life, offers the potential for easier dose titration and showed similar improvements in Phase 3 compared with mavacamten.^{62,63} While current data support their use as add-on or second-line agents, future trials, such as the MAPLE study, may clarify their role as potential first-line therapy.⁴⁹ Echocardiographic monitoring of LVEF is essential, particularly within the first 12 weeks of treatment. NT-proBNP levels may provide early indication of treatment response, and serial assessment every 6 months is reasonable. Mavacamten should be temporarily withheld in cases of LVEF decline <50%, with re-initiation at a lower dose once function normalizes and obstruction recurs.^{7,64,65} In patients with recent myocardial infarction and reduced LVEF or newly diagnosed Takotsubo cardiomyopathy, CMI therapy should generally be withheld. Re-initiation may be considered once LVEF has recovered to >50% and significant LVOT obstruction (≥ 30 mmHg) is confirmed, preferably starting at the lowest effective dose. Management in these complex scenarios should involve a multidisciplinary heart team. Response to CMI therapy should not be defined solely by absolute reduction in LVOT gradient, but by an integrated assessment of symptom improvement (e.g. NYHA class), exercise tolerance, biomarkers (NT-proBNP, Troponin), and imaging-based parameters such as LV mass regression or diastolic function. Currently, no validated thresholds exist to define non-response, and treatment decisions should be individualized. In non-responders, anatomic contributors to obstruction should be reassessed through TEE, CMR, or invasive haemodynamic evaluation. In patients with confirmed oHCM and persistent obstruction despite optimized medical therapy, SRT, including surgical myectomy or ASA, should be considered.

Drug trials in nHCM

While therapeutic advancements in oHCM have been substantial, evidence-based treatment options for nHCM remain limited. CMIs have been investigated in this subgroup. The phase II MAVERICK-HCM trial demonstrated biomarker reduction with mavacamten but no significant improvement in functional parameters.⁸ The phase III ODYSSEY-HCM trial investigating mavacamten in symptomatic nHCM did not meet its dual primary endpoints, change in peak oxygen consumption (pV_{O_2}) and Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS), at 48 weeks.⁶⁶ While these findings underscore the complexity of treating nHCM, subgroup analyses are ongoing and may yield clinically relevant insights. Recently, a phase II trial of aficamten in symptomatic nHCM demonstrated favourable safety and tolerability, with numerical improvements in pV_{O_2} , KCCQ-CSS, and NT-proBNP compared with placebo, supporting further investigation in larger trials.⁶⁷

The ACACIA-HCM trial (NCT06081894) is currently evaluating aficamten in this population. Additionally, sacubitril/valsartan was assessed in a phase II randomized controlled trial (SILICOFM-Trial) but failed to show improvement in pV_{O_2} or natriuretic peptides, despite theoretical benefits on myocardial remodelling.⁶⁸ Collectively, these studies highlight both the substantial unmet need and the continued efforts to define effective, mechanism-targeted therapies in nHCM.

EDG-7500, a novel cardiac sarcomere modulator, has shown promising results in the Phase II CIRROS-HCM trial, with early improvements in gradients and symptoms.^{69,70} Recently, the IMPROVE-HCM trial evaluated the metabolic modulator nineraxstat in symptomatic nHCM, demonstrating good safety and improved ventilatory efficiency.⁷¹ Post hoc analysis suggested potential benefit in patients with greater symptom burden.⁷¹ The clinical relevance of these agents remains to be determined and will require confirmation in larger phase IIb/III trials.⁷²

Septal reduction therapy

In patients with oHCM who remain symptomatic despite optimized pharmacologic therapy, Septal reduction therapy (SRT) is recommended.⁶ The goal is to alleviate LVOT obstruction by reducing septal thickness and thereby improving symptoms, functional status, and quality of life. Surgical septal myectomy and ASA are the two established SRT modalities.⁷³ The choice of procedure is based on anatomical considerations, patient preference, centre expertise, and comorbidities.^{73–75} The selection of patients and the choice between myectomy and ASA should occur within multidisciplinary HCM teams. The availability of dedicated imaging, surgical, and interventional expertise is essential. The ESC and AHA guidelines emphasize that outcomes are superior in centres performing a high volume of HCM interventions.^{6,11} Based on expert consensus, a minimum institutional volume of ≥ 10 septal reduction procedures per year is suggested to support procedural safety, sustain operator proficiency, and optimize clinical outcomes.

SRT may be proactively considered in symptomatic women of childbearing age who are planning pregnancy and in whom CMI are contraindicated. However, SRT is not routinely recommended in asymptomatic women; instead, close clinical monitoring during pregnancy is advised due to the high-risk nature of gestation in oHCM.⁷⁶ SRT may also be appropriate in selected patients who are unwilling or unable to pursue long-term pharmacologic therapy.

Surgical myectomy is the preferred intervention in patients with oHCM who present with concurrent structural abnormalities requiring correction, such as mitral valve disease, anomalous papillary muscles, or abnormalities of the subvalvular apparatus, or the need for concomitant coronary artery bypass grafting due to multivessel CAD.^{77–80} It is also indicated in patients with persistent symptoms despite optimized medical therapy when a suitable septal branch for ASA is absent. The procedure involves surgical resection of the hypertrophied interventricular septum, typically via a transaortic approach, and is performed in experienced centres with dedicated HCM surgical programs.^{77,81} When conducted in high-volume institutions, myectomy offers durable LVOT gradient reduction, substantial symptom relief, and long-term clinical stability.⁷³ In some oHCM patients with significant obstruction but no severe septal hypertrophy, in which the mechanism of obstruction is mainly related to abnormal morphology and function of mitral valve, a shallow myectomy with extensive remodelling of mitral apparatus is recommended in expert dedicated centres.⁸²

ASA is a minimally invasive, catheter-based intervention aimed at reducing LVOT obstruction in patients with oHCM. The procedure involves the targeted injection of ethanol into a septal perforator branch of the left anterior descending artery, resulting in a controlled myocardial infarction that leads to thinning of the hypertrophied septal myocardium and subsequent LVOT gradient reduction.⁸³ ASA is typically considered in patients who are poor surgical candidates or who prefer a less invasive alternative to surgical myectomy, provided that suitable septal anatomy is present.⁸⁴ Optimal patient selection is essential, and the procedure should be performed in experienced centres with dedicated HCM programs to ensure procedural safety and efficacy.⁴ A key limitation of ASA is its association with conduction system disturbances, particularly complete heart block, often necessitating permanent pacemaker implantation. Reported pacemaker implantation rates post-ASA range from ~9% to 20%, depending on patient characteristics, technique, and center experience.^{85,86} The presence of an existing pacemaker or ICD may favour ASA by reducing concerns related to procedure-induced conduction disturbances. Although both surgical myectomy and ASA provide effective and durable relief of LVOT obstruction when performed by experienced centres, long-term surveillance remains essential. Data from the international SHARE Registry demonstrated that, despite successful gradient reduction in >90% of patients, ~13% experienced a heart failure composite outcome during extended follow-up, often in the absence of residual obstruction.⁸⁷

Importantly, the risk of late heart failure events was higher after ASA (16%) compared with myectomy (12%). Older age at intervention, female sex, and childhood SRT were additional predictors of adverse outcomes. These findings emphasize that SRT alleviates the mechanical component of obstruction but does not alter the underlying cardiomyopathic substrate, underscoring the need for structured, lifelong follow-up even after apparently successful procedures.⁸⁷

Emerging techniques such as percutaneous radiofrequency septal ablation and hybrid minimally invasive surgical approaches are under active investigation as potential alternatives or adjuncts to established septal reduction therapies. These modalities may expand treatment options, particularly for patients with mid-ventricular or apical obstruction who are not ideal candidates for surgical myectomy or ASA.^{88–92} While early results are encouraging, these approaches remain investigational and should currently be reserved for use within experienced centres or clinical trial settings. Multicenter data and long-term outcomes are needed before routine clinical adoption can be recommended. Additionally, the role of beating-heart myectomy and other hybrid techniques warrants further evaluation in select patient populations.

Comorbidities and subpopulations

HCM often coexists with other cardiovascular and systemic conditions that may alter its clinical course complicate diagnosis, or impact management. A patient-centred, holistic approach is essential, especially in older adults and those with multimorbidity. Below, we address some of the major co-morbidities.

Atrial fibrillation

Atrial fibrillation (AF) is the most common arrhythmia in HCM (around 25% prevalence) and is associated with worsening symptoms, thromboembolic risk, and adverse prognosis. Anticoagulation with direct oral anticoagulants (DOACs) is recommended regardless of CHA₂DS₂-VASc score.⁵ Rhythm control may be considered, including antiarrhythmic drugs or catheter ablation, though success rates are modest due to structural remodelling. For rate control, BB or non-dihydropyridine CCBs are preferred over digoxin, given the potential risk of worsening LVOT obstruction. Catheter ablation may be considered earlier in the disease course, including in selected patients with paroxysmal or minimally symptomatic AF, to reduce the risk of atrial remodelling, symptom progression, and heart failure decompensation.⁹³ Emerging data suggest that patients with HCM in sinus rhythm but with marked left atrial enlargement may carry an elevated risk of thromboembolic events. A left atrial diameter ≥ 48 mm has been associated with increased stroke risk, even in the absence of documented atrial fibrillation.⁹⁴ While routine anticoagulation is not currently recommended in this setting, it may be considered on an individual basis in selected high-risk patients with severely enlarged atria and additional risk factors or suspected subclinical AF. Ongoing studies and registry data may further refine risk stratification in this subgroup.

For rhythm control in HCM, preferred agents are—besides BB with limited efficacy—amiodarone, sotalol, and dofetilide (where available).^{95,96} Disopyramide is an additional option in oHCM, as it combines rhythm control with gradient reduction, typically in combination with a β -blocker or CCB. Class IC drugs (flecainide, propafenone) are contraindicated due to proarrhythmic risk in structural heart disease. Amiodarone remains the drug of choice, particularly in patients with ICDs and recurrent VT/VF or frequent shocks, while sotalol may be considered in selected patients with less severe arrhythmia burden. Raising potassium levels was recently demonstrated to reduce arrhythmic burden in ICD carriers with HF-rEF and should be considered in arrhythmic HCM patients, too.⁹⁷ Other antiarrhythmic drugs have limited data and less favourable safety profiles in HCM.⁹⁵

Hypertension

Hypertension is a prevalent comorbidity in patients with HCM, particularly among older individuals. Effective management necessitates a nuanced approach that considers the presence or absence of LVOT obstruction, as the haemodynamic responses to antihypertensive therapies can vary significantly between oHCM and nHCM phenotypes.^{4,16} In nHCM, antihypertensive treatment should generally follow standard hypertension guidelines, with particular attention to agents that support diastolic function, address presence of systolic dysfunction/heart failure and mitigate adverse remodelling (Figure 1).⁹⁸ β -blocker are often utilized for their negative chronotropic effects, which enhance diastolic filling and reduce myocardial oxygen demand, but are accompanied by little symptomatic benefit.⁹⁹ Non-dihydropyridine CCBs, such as verapamil and diltiazem, serve as alternatives or adjuncts, offering similar benefits in heart rate control and diastolic improvement. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) may be employed for their favourable effects on blood pressure control and ventricular remodelling. Mineralocorticoid receptor antagonists (MRAs) can further aid in addressing myocardial fibrosis and improving diastolic function.^{100,101} Management of hypertension in oHCM is significantly more complex. In these patients, afterload reduction and pre-load depletion, can paradoxically worsen LVOT obstruction, leading to hypotension, syncope, or worsening dyspnoea. Therefore, blood pressure treatment must be carefully titrated with a focus on preserving haemodynamic stability.¹⁰¹ Early initiation of CMI may facilitate more effective blood pressure management by reducing LVOT gradients.¹⁰² BB and non-dihydropyridine CCBs remain the preferred initial agents. Cautious, individualized titration of ACE inhibitors or ARBs can be considered, with close haemodynamic monitoring. The use of MRAs may also be acceptable in selected cases, although evidence is limited. Centrally acting α_2 -agonists (e.g. clonidine, moxonidine) and α_1 -blockers (e.g. prazosin, doxazosin) carry a risk of hypotension and should generally be avoided unless used with extreme caution under close gradient surveillance (Table 1).⁴⁷

Coronary artery disease

Coronary artery disease (CAD) is an important and often under-recognized comorbidity in patients with HCM, particularly in the elderly population.⁷⁴ Studies have reported that up to 20% of older HCM patients may have coexistent obstructive epicardial coronary disease, which can significantly impact symptoms, prognosis, and therapeutic decision-making.³⁸ The presence of CAD can exacerbate angina, dyspnoea, and arrhythmias, and is associated with increased risk of adverse outcomes, including heart failure progression and SCD.³⁸ It is critical to distinguish between microvascular ischaemia, which is intrinsic to HCM due to small-vessel dysfunction and myocardial hypertrophy, and epicardial CAD, which requires separate evaluation and treatment.¹⁰³ BB are the cornerstone of symptomatic treatment in both HCM and CAD, providing relief of angina, improvement in diastolic filling, and gradient reduction in oHCM.¹⁰⁴ For patients who are intolerant to BB, non-dihydropyridine CCBs (e.g. verapamil, diltiazem) may be considered as alternative therapy.¹⁰⁵ In patients with concomitant epicardial CAD, CMI are not contraindicated but should only be initiated when LVEF is preserved ($\geq 55\%$) and with close echocardiographic monitoring, as their negative inotropic effect may precipitate systolic dysfunction in ischaemic myocardium.⁶ Vasodilators frequently used for CAD, such as long-acting nitrates or dihydropyridine CCBs, can worsen LVOT obstruction and should generally be avoided in oHCM,⁵¹ unless obstruction has been controlled (e.g. following CMI therapy or septal reduction).

While vascular inflammation and microvascular dysfunction are increasingly recognized in HCM, there is currently insufficient evidence to support HCM-specific LDL cholesterol thresholds. Until further data become available, lipid management should follow standard

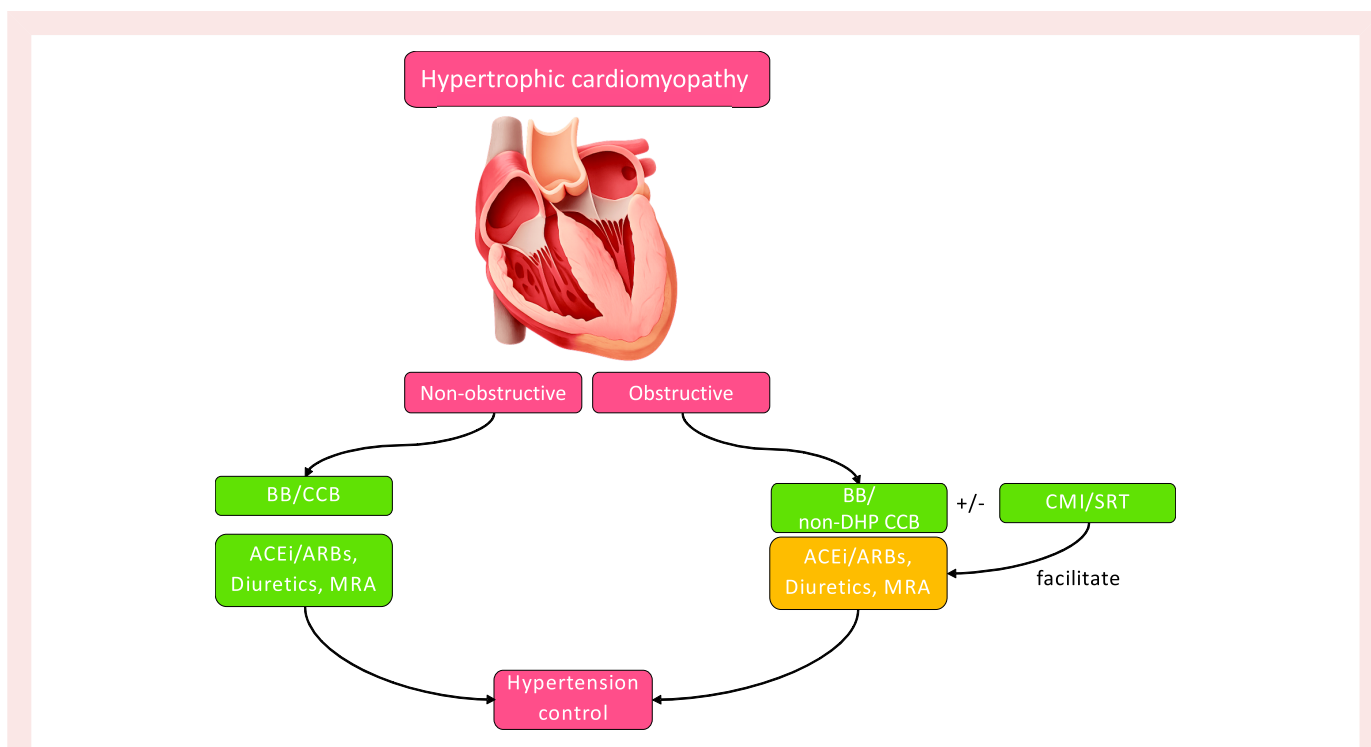


Figure 1 Suggested approach to hypertension control in patients with hypertrophic cardiomyopathy. In non-obstructive HCM, beta-blockers or calcium channel blockers are first-line therapy for hypertension, with angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, diuretics, or mineralocorticoid receptor antagonists added as needed. In obstructive HCM, BB or non-dihydropyridine CCB remain first-line, while ACEi/ARBs, diuretics, and MRAs should be used cautiously due to the risk of worsening LVOT obstruction. In such patients, cardiac myosin inhibitors or septal reduction therapy can reduce obstruction and facilitate more effective and safer blood pressure management

cardiovascular guidelines, with treatment individualized based on overall atherosclerotic cardiovascular risk rather than HCM diagnosis alone.

Diabetes mellitus and metabolic syndrome

Diabetes mellitus (DM) and metabolic syndrome are prevalent in HCM, particularly in older adults, and contribute to adverse myocardial remodelling, increased fibrosis, and impaired diastolic function. Optimized glycemic control remains essential, but the cardiovascular impact of these comorbidities extends beyond glucose levels. Sodium-glucose cotransporter 2 (SGLT2) inhibitors, though developed as antidiabetic agents, have consistently reduced cardiovascular death and heart failure hospitalizations across the EF spectrum, including heart failure with preserved ejection fraction (HFpEF), irrespective of diabetic status.^{106–108} Although major HFpEF trials did not specifically target HCM, they included patients with structural heart disease overlapping with nHCM phenotypes.^{107,109} As a result, SGLT2 inhibitors are increasingly considered in symptomatic nHCM patients with HFpEF-like physiology, even in the absence of diabetes, based on extrapolated evidence from these studies. The ongoing SONATA-HCM trial, which includes both obstructive and non-obstructive HCM cohorts, is expected to provide more definitive insights into the role of SGLT2 inhibitors in this specific population.¹¹⁰ Until such targeted data become available, the use of SGLT2 inhibitors may be reasonable in selected nHCM patients, particularly when features of HFpEF and metabolic syndrome are present.

Heart failure management in HCM

Heart failure in HCM spans a wide spectrum, from HFpEF physiology driven by diastolic dysfunction, restriction and microvascular ischaemia

to advanced HCM with LV systolic dysfunction (end-stage HCM). In patients with HFpEF physiology, management should focus on maintenance of euolemia, careful use of diuretics, blood pressure control, and consideration of SGLT2 inhibitors, which have demonstrated robust benefit in HFpEF irrespective of diabetes.⁵ In advanced HCM with LVEF <50%, standard guideline-directed HFpEF therapy is recommended, including BB, ACE inhibitors or ARBs, MRAs, and SGLT2 inhibitors.⁵ Device therapy, including ICD and cardiac resynchronization therapy (CRT), should be applied according to standard indications. In refractory cases, candidacy for heart transplantation must be evaluated, and management is best co-ordinated in expert centres with access to advanced heart failure therapies and transplant programs.

Pregnancy

Pregnancy is generally well-tolerated in women with HCM; however, it requires careful pre-conception counselling and multidisciplinary monitoring throughout gestation.^{111–113} Physiological adaptations during pregnancy, particularly increased blood volume and cardiac output, can exacerbate LVOT gradients and trigger arrhythmias.^{114,115} In women with HFpEF-like physiology, limited diastolic compliance may impair preload accommodation, increasing the risk of volume overload and decompensation, especially in late gestation.¹¹⁶ According to the 2025 ESC Guidelines for the Management of Cardiovascular Disease and Pregnancy, most women with HCM fall into mWHO class II–III and should be managed within a dedicated Pregnancy Heart Team, particularly if significant LVOTO, prior arrhythmia, or systolic dysfunction is present.¹¹⁷ BB remain the first-line treatment for symptom control and prevention of arrhythmia; atenolol should be avoided because of its association with fetal growth restriction, whereas metoprolol or bisoprolol are preferred.^{118,119} Close fetal monitoring is essential when

Table 1 Antihypertensive medication in hypertrophic cardiomyopathy

Drug class	Class examples	Suitability in nHCM	Suitability in oHCM	Key considerations
Beta-blockers	Bisoprolol Metoprolol	First-line	First-line	Reduces HR, improves diastolic filling; avoid in severe bradycardia
Non-dihydropyridine CCBs	Verapamil Diltiazem	Alternative	Alternative	Negative chronotropy; avoid in severe bradycardia
Dihydropyridine CCBs	Amlodipine Lercanidipine	Second-line	Not recommended	Worsening LVOT obstruction due to afterload reduction
ACE inhibitors/ARBs	Ramipril, Lisinopril Candesartan, Valsartan	Remodelling benefit	Cautious use	Afterload reduction may worsen obstruction
Mineralocorticoid receptor antagonists	Spironolactone Eplerenone	Fibrosis attenuation	Cautious use	Monitor K ⁺ and renal function; hypotension risk in oHCM
Diuretics	Torsemide, Furosemide Hydrochlorothiazide	As needed for volume	With caution	Avoid volume depletion in oHCM; risk of hypotension
Centrally acting agents	Clonidine Moxonidine	Not preferred	High-risk	Bradycardia, hypotension; generally avoided
Alpha-1 blockers	Doxazosin Prazosin	Third-line	Not recommended	Vasodilatory collapse risk in oHCM
Direct vasodilators (Hydralazine)	Hydralazine	Rare use	Avoid	Marked vasodilation may worsen gradient
Cardiac myosin inhibitors	Mavacamten Aficamten	Not for BP	Facilitator	Reduces gradient; allows introduction of conventional antihypertensives

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; CMI, cardiac myosin inhibitor; HR, heart rate; HCM, hypertrophic cardiomyopathy; LVOT, left ventricular outflow tract; nHCM, non-obstructive hypertrophic cardiomyopathy; oHCM, obstructive hypertrophic cardiomyopathy.

BB is prescribed, and dose adjustments may be necessary to balance maternal and fetal needs. Baseline assessment of NT-proBNP and high-sensitivity troponin may offer useful reference points. Serial measurements may support clinical decision-making in selected cases, especially when new or worsening symptoms arise, though more evidence is needed. Vaginal delivery is feasible in most cases, unless contraindicated by obstetric or cardiovascular factors. Caesarean delivery may be considered in the setting of severe LVOT obstruction, heart failure, or anticoagulation use.¹²⁰ Delivery planning should involve a multidisciplinary team including cardiologists, obstetricians, and anaesthesiologists to ensure optimal maternal and fetal outcomes.¹²⁰ In rare cases of decompensated oHCM during pregnancy refractory to medical therapy, ASA may be considered as a last-resort option.^{76,121} However, experience with ASA in pregnancy is limited, and it should only be performed in high-volume centres with expertise in HCM and maternal cardiac care. Routine ICD interrogation before delivery is advised, and fetal harm from maternal ICD shocks appears unlikely. In the event of cardiac arrest after 20 weeks of gestation, left-lateral uterine displacement should be performed to avoid aortocaval compression, and caesarean delivery should be initiated if spontaneous circulation is not restored within 4 min.¹¹⁷ Postpartum surveillance remains critical, as haemodynamic stress and arrhythmia risk may persist or emerge after delivery.¹²⁰

Paediatric and adolescent HCM

HCM in paediatric and adolescent populations often manifests with a more aggressive disease course, particularly in cases associated with syndromic or metabolic aetiologies.¹²² Risk stratification and management are challenging due to the limited applicability of adult-derived risk factors and the absence of well-established guidelines for ICD

implantation in this demographic. Notably, the HCM Risk-Kids model has been developed and externally validated to predict SCD risk in children, offering a tool tailored to the paediatric population.^{123,124} However, further research is imperative to refine paediatric-specific risk assessment tools and management strategies.

Genetic testing is recommended in children with a family history of HCM or phenotypic evidence of disease, with cascade screening extended to first-degree relatives. In genotype-positive/phenotype-negative children, longitudinal surveillance with ECG and echocardiography every 1 to 3 years is generally advised, with shorter intervals during puberty due to accelerated phenotypic evolution. The HCM Risk-Kids model, which incorporates clinical variables such as maximal wall thickness, left atrial size, LVOT gradient, unexplained syncope, and non-sustained ventricular tachycardia, has undergone large-scale external validation, confirming its ability to provide individualized 5-year SCD risk estimates.¹²⁵ A threshold of $\geq 6\%$ predicted 5-year risk identified more than 70% of SCD events, offering discriminatory performance superior to prior guideline-based approaches.¹²⁵ Current expert consensus supports ICD implantation in children with a Risk-Kids estimated 5-year SCD risk $\geq 6\%$, in those with malignant ventricular arrhythmias, unexplained syncope, massive hypertrophy (wall thickness Z-score > 6 or ≥ 30 mm), or a strong family history of early SCD. These considerations highlight the importance of integrating genetic testing, structured follow-up, and individualized risk prediction into the management of paediatric HCM, alongside multidisciplinary decision-making and careful reassessment during growth and development.

Emerging preclinical studies utilizing induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) from paediatric HCM patients have demonstrated that CMIs can reverse hypertrophic phenotypes, effectively mirroring the effects of genetic variant correction.¹²⁶ Additionally, recent data suggest that patients with mild oHCM

symptoms derive similar benefit from CMI as those with more advanced disease, with improvements in exercise capacity, gradients, and NT-proBNP levels.¹²⁷ Elevated NT-proBNP may serve as an early disease marker and potential indicator for treatment initiation, particularly given the NT-proBNP-lowering effects of CMI.¹²⁸ These findings support the potential utility of CMI in paediatric HCM, although their safety and efficacy in children are still under investigation. Ongoing trials such as SCOUT-HCM (NCT06253221) and CEDAR-HCM (NCT06412666) are evaluating mavacamten and aficamten, respectively, in adolescents with symptomatic oHCM, aiming to fill this critical evidence gap.

Controversies and areas of uncertainty

Despite substantial progress in the diagnosis, risk stratification, and treatment of HCM, several clinically relevant areas remain controversial or insufficiently supported by evidence to permit uniform recommendations. These unresolved issues underscore the need for ongoing research and expert consensus to improve individualized care strategies.

Risk stratification for sudden cardiac death

The optimal strategy for stratifying risk of SCD in HCM remains a subject of international debate. While the ESC 5-year risk score, based on multiple conventional clinical risk markers, is widely implemented in European practice, U.S. guidelines favour individualized assessment without a composite scoring tool.^{4,86} A key area of ongoing controversy is the role of LGE on CMR, particularly when LGE exceeds 15% of LV mass. The prognostic weight of LGE in guiding ICD decisions is not uniformly agreed upon across guidelines.

In practice, ICD implantation should be guided by the ESC 5-year SCD risk calculator as a starting point, integrated with individualized clinical judgment as emphasized by the 2024 AHA/ACC guidelines. In patients with high calculated risk ($\geq 6\%$), ICD implantation is generally recommended, whereas in low-risk individuals ($< 4\%$) it is not. In borderline cases (4%–6%), additional factors such as extensive LGE ($> 15\%$), apical aneurysm, or pathogenic sarcomeric variants should be carefully considered, as they may shift the balance toward implantation, providing important information for shared decision-making with patients (Figure 2). This hybrid strategy reconciles regional guidelines and reflects contemporary expert consensus, ensuring that device therapy is targeted to those most likely to benefit while avoiding unnecessary exposure to long-term ICD complications.

Given these differences, there is broad expert support for developing a unified, hybrid risk stratification framework that integrates established clinical scores, quantitative LGE assessment, and emerging genetic and imaging biomarkers. Such a pathway would reconcile regional disparities and incorporate state-of-the-art data. However, the approach must retain flexibility to allow individualized decision-making that balances lifetime risks of device therapy against competing clinical risks, consistent with a shared decision-making model.

Management of asymptomatic obstructive HCM

The management of asymptomatic oHCM with high resting or provokable LVOT gradients (≥ 50 mmHg) remains controversial. Current guidelines do not support pharmacological treatment or SRT in the absence of symptoms.⁶ However, close surveillance is warranted, as patients may underestimate or adapt to their symptoms. Objective assessment of exercise capacity, using cardiopulmonary exercise testing or stress echocardiography, can help unmask functional limitation. While no proven indication for invasive therapy exists in asymptomatic

patients, selected cases with progressive left atrial enlargement, pulmonary hypertension, or declining exercise tolerance may merit earlier intervention. Emerging pharmacologic strategies, particularly CMI, have demonstrated robust gradient reduction and favourable remodelling in symptomatic oHCM and are now being studied in broader patient populations.^{129,130} Evidence of reverse remodelling and stabilization of fibrosis further raises the possibility that these agents may offer disease-modifying benefits even in minimally symptomatic or asymptomatic individuals. Until such data are available, management should remain focused on structured surveillance, early recognition of clinical change, and shared decision-making within expert HCM programs.

Genotype-positive, phenotype-negative individuals

Management of individuals who carry a pathogenic or likely pathogenic variant but lack overt LVH remains undefined.¹³¹ There is currently no consensus on the optimal monitoring frequency, imaging modality, or preventive interventions in this population. Whether such individuals benefit from lifestyle counselling, structured physical activity recommendations, or advanced imaging (e.g. CMR with mapping) is unresolved. Current expert consensus endorses a flexible screening interval of 1 to 3 years, including routine ECG and echocardiography combined with comprehensive cardiovascular risk management. Surveillance frequency should be tailored to individual factors such as familial variant penetrance, age of onset, and sex-specific disease expression. This personalized strategy seeks to optimize early detection while minimizing the burden of monitoring in asymptomatic carriers.

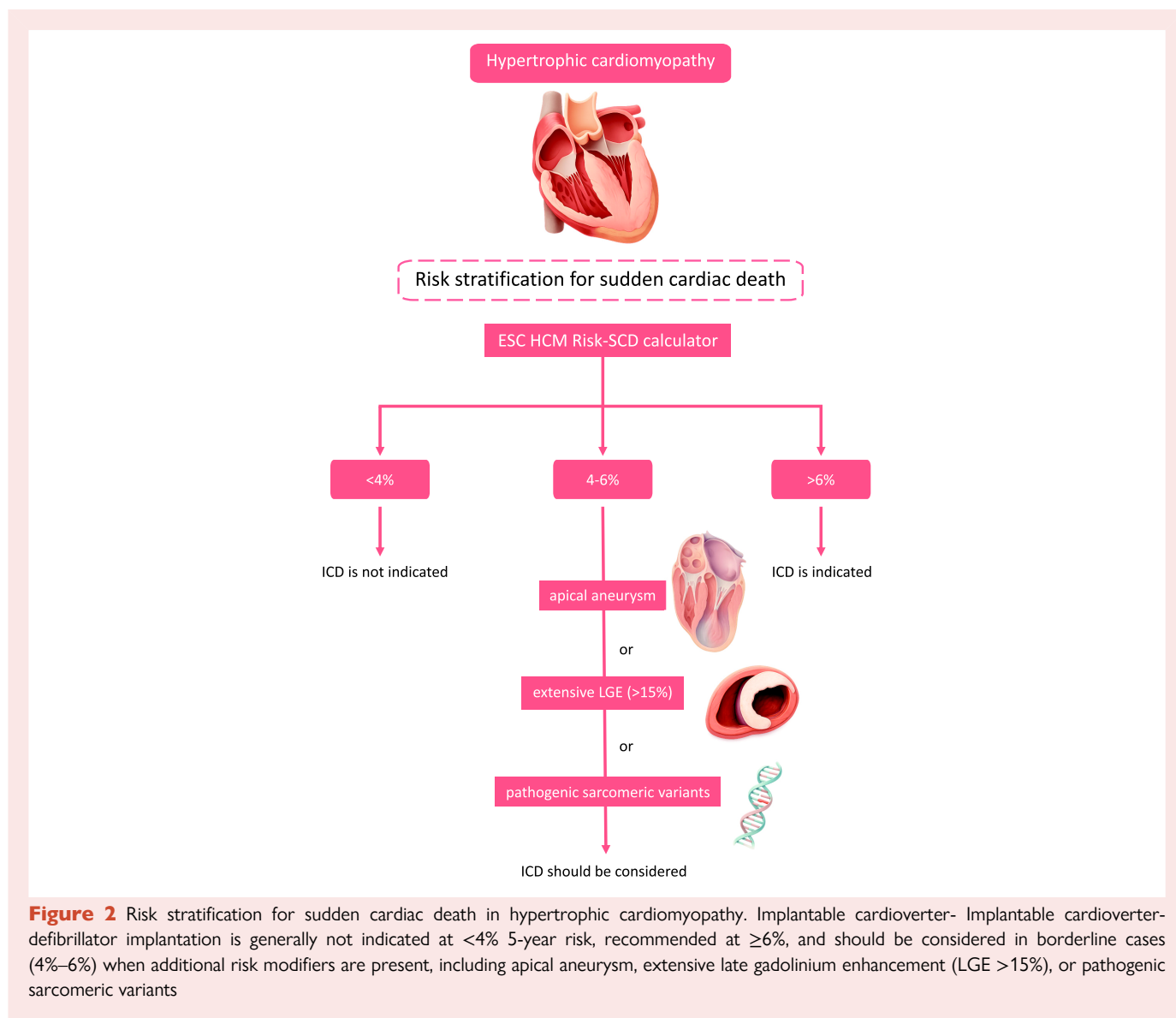
Role of exercise in HCM

Exercise recommendations in HCM have evolved significantly from historically restrictive guidance to more nuanced, individualized assessments.^{132,133} Emerging data suggest that moderate-intensity recreational exercise may be safe and potentially beneficial, even in genotype-positive individuals without clinical disease.¹³⁴ However, uncertainties persist regarding the upper safety limit for competitive sports, and robust prospective data on long-term outcomes remain limited. For low-risk HCM patients, moderate-intensity recreational exercise should typically be encouraged as part of a healthy lifestyle, unless specific clinical factors contraindicate it.¹³⁵ This aligns with emerging data indicating that mild-to-moderate exercise does not present significant risks and may offer benefits for both physical and psychological well-being. Shared decision-making is particularly important when considering high-intensity exercise or competitive sports, where individual risk factors, including family history, symptoms, genetic variants, and disease progression, should be carefully evaluated. Beyond clinical considerations, further research is needed to understand the psychological and social impacts of exercise restrictions, especially in younger patients. Restrictions may negatively affect quality of life, and balancing the benefits of physical activity with psychosocial well-being should be an integral part of HCM management.¹³⁵ This underscores the importance of individualized care that takes into account both physical and emotional health.

Future directions

Advancements in the understanding of HCM, coupled with technological innovations, present opportunities to enhance diagnosis, personalize treatment, and improve patient outcomes. Several key areas are poised to shape the future landscape of HCM care.

The progression of genomics and molecular cardiology is anticipated to facilitate genotype-specific management strategies for HCM.¹³⁶ Distinguishing between pathogenic variants, likely pathogenic variants, and variants of uncertain significance (VUS) is becoming increasingly critical. Emerging gene-editing technologies, such as CRISPR/Cas9, are



under exploration in preclinical settings for their potential to correct specific genetic mutations associated with HCM.^{137–139} Future HCM management may incorporate transcriptomics, proteomics, and metabolomics to identify disease-modifying pathways and predict clinical trajectories.¹⁴⁰ Emerging biomarkers, including fibrosis markers, circulating microRNAs, and high-sensitivity troponins, may assist in early detection and monitoring of disease progression. However, more data are needed before widespread clinical implementation of these biomarkers.

Artificial Intelligence (AI) algorithms are being developed to enhance image interpretation, risk stratification, and automated phenotyping using multimodal data, including ECG, echocardiography, and CMR.^{141–144} These tools have the potential to facilitate early diagnosis in primary care settings and improve the precision of therapeutic decisions. In the context of HCM care, AI could have its greatest impact in managing the growing cohort of genotype-positive, phenotype-negative individuals, who require stratified screening pathways. AI-driven approaches could facilitate tailored surveillance in this population, improving the identification of at-risk patients even before clinical symptoms manifest. Risk stratification using imaging data and ECGs may offer the most immediate benefit, helping clinicians make more informed decisions regarding interventions

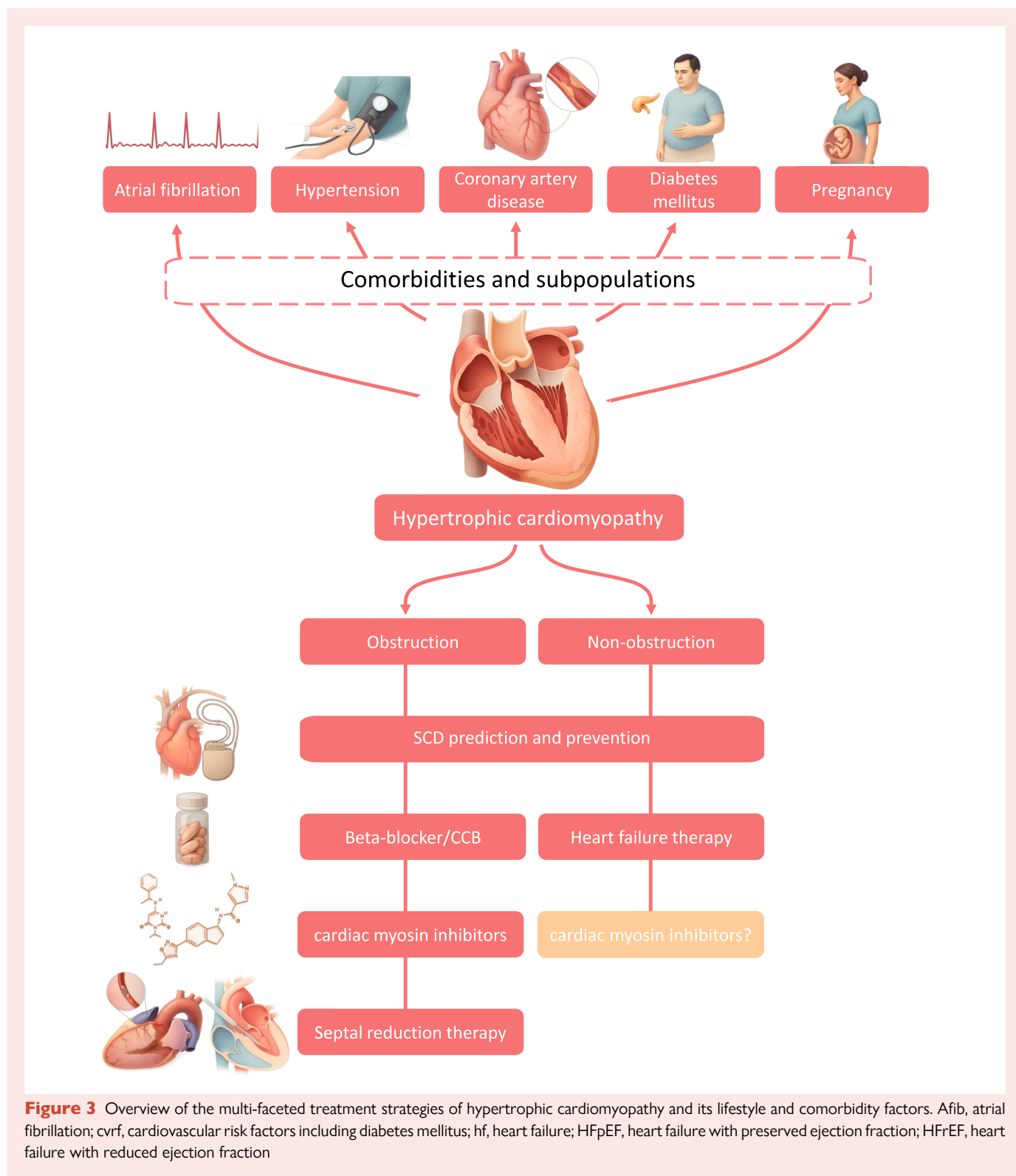
such as ICD implantation or pharmacologic therapy.^{145,146} Recent prospective and validation studies have confirmed the feasibility of such approaches. At the Cleveland Clinic, real-world use of an FDA-approved AI-ECG platform (Viz-HCM) in over 45 000 patients achieved sensitivities up to 95% and specificities >98%, identifying 5% of patients with a new HCM diagnosis who had previously eluded clinical detection.¹⁴⁷ However, significant barriers remain to the integration of AI tools into routine cardiology practice.¹⁴⁸ Challenges include data quality, as AI models rely on large, high-quality datasets, interpretability of AI decisions (especially in clinical contexts), and regulatory issues surrounding AI implementation in medical practice. The absence of standardized data formats and limited interoperability between imaging systems and electronic health records further constrain scalability, while concerns about algorithm transparency underscore the need for explainable AI. Moreover, ensuring ethnic diversity and inclusivity in AI datasets is essential to ensure that AI algorithms are generalizable across diverse populations, avoiding bias that could lead to disparities in healthcare delivery.

Adaptive trial designs and pragmatic studies are needed to evaluate new therapies efficiently in diverse populations, including paediatric and elderly patients. Integration of real-world data from registries and digital health platforms will complement traditional randomized

Table 2 Increasing body of evidence for myosin-inhibition

Trial name	Phase	Intervention	Population	Primary endpoint(s)	Key findings
ACACIA-HCM	3	Aficomten	Symptomatic nHCM	Change in KCCQ and pVO ₂	ongoing
CEDAR-HCM	2/3	Aficomten vs. Placebo	Pediatric symptomatic oHCM	Change in LVOT gradient (Valsalva)	Ongoing
CIRRUS-HCM	2	EDG-7500	Symptomatic oHCM and nHCM	Safety, tolerability	Reduced LVOT gradients, well-tolerated
EXPLORER-HCM	3	Mavacamten vs. Placebo	Symptomatic oHCM	Change in pVO ₂	Improved exercise capacity
FOREST-HCM		Aficomten	oHCM and nHCM	Long-term effects of Aficomten	Ongoing
IMPROVE-HCM	2	Nineraxstat vs. Placebo	nHCM	Safety and tolerability	Safe and well-tolerated
MAVA-LTE		Mavacamten	oHCM	Long-term effects of Mavacamten	Ongoing
MAPLE-HCM	3	Aficomten vs. Metoprolol	Symptomatic oHCM	Change in pVO ₂	Aficomten significantly improved exercise capacity, symptoms, LVOT gradient, and QoL vs. metoprolol
MAVERICK-HCM	2	Mavacamten	nHCM	safety and efficacy of Mavacamten	Well-tolerated, reduction in NT-proBNP
ODYSSEY-HCM	3	Mavacamten vs. Placebo	Symptomatic nHCM	Change in KCCQ, pVO ₂	No significant improvement in quality of life or exercise capacity
PIONEER-HCM	2	Mavacamten	Symptomatic oHCM	safety and efficacy of Mavacamten	reduce LVOT obstruction and improve symptoms
REDWOOD-HCM	2	Aficomten vs. Placebo	Symptomatic HCM	Safety and tolerability of Aficomten	Aficomten appears to be a safe and efficacious therapy
SCOUT-HCM	3	Mavacamten vs. Placebo	Symptomatic adolescents oHCM	Change in LVOT (Valsalva)	ongoing
SEQUOIA-HCM	3	Aficomten vs. Placebo	Symptomatic oHCM	Change in pVO ₂	significantly greater improvement in pVO ₂
VALOR-HCM	3	Mavacamten vs. SRT	Severe symptomatic oHCM	composite of decision to proceed with SRT or eligibility for SRT	Reduced symptoms, reduction in SRT need

HCM, hypertrophic cardiomyopathy; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVOT, left ventricular outflow tract; NT-proBNP, N-terminal pro-B-type natriuretic peptide; oHCM, obstructive hypertrophic cardiomyopathy; nHCM, non-obstructive hypertrophic cardiomyopathy; pVO₂, peak oxygen consumption; QoL, quality of life; SRT, septal reduction therapy.



controlled trials (RCTs).^{149,150} In recent years, a number of clinical trials have been completed, with several ongoing, focused on novel treatments for HCM (Table 2). A comprehensive summary of these studies, including key trial designs, patient populations, primary endpoints, and results, is presented in Table 2. This growing body of evidence is expected to inform future treatment strategies and contribute to the evolution of clinical practice in HCM care.

Patient-reported outcomes and shared decision-making

There is an increasing emphasis on incorporating the patient's perspective in therapeutic decision-making.⁶ Tools to systematically capture patient-reported outcomes, such as symptoms, functional status, and treatment preferences, are essential for achieving holistic and patient-centred care.

While tools like the Kansas City Cardiomyopathy Questionnaire (KCCQ) have been widely used, they may not fully capture the breadth of symptoms experienced by HCM patients, particularly those related to chest pain and pre-syncope.¹⁵¹ The NYHA classification, which is commonly used, has also been criticized for its limitations in evaluating HCM-specific symptoms and functional capacity.¹⁵² Emerging wearable technologies and remote monitoring offer the potential to better capture a patient's daily experiences, providing continuous data that could improve symptom tracking and treatment adjustments.³⁷ Furthermore, novel approaches such as epigenetic modulation or immune-targeted therapies could play a role in modifying disease phenotypes and offering more personalized treatment options in the future. Given these gaps in current tools and technologies, there is a clear need for HCM-specific patient-reported outcomes that comprehensively address the disease's multi-faceted impact on patients, including symptoms beyond heart failure, such as chest pain, syncope, and exercise intolerance. The development of these tools, along with integration of emerging technologies, will be critical in advancing patient-centred care for HCM.

Summary

The therapeutic options in HCM have expanded considerably over the past years. This makes precise understanding and diagnosis of thick hearts even more important to guide specific treatments summarized in Figure 3. This consensus document is a shared opinion of a multidisciplinary team with the aim to stimulate research in areas with yet little evidence and practical suggestions to real-world issues when treating HCM patients.

Author contributions

Benjamin Meder (Conceptualization; Investigation; Supervision; Visualization; Writing—original draft; Writing—review & editing), Caroline J Coast (Writing—review & editing), Leslie A Leinwand (Writing—review & editing), Maurizio Pieroni (Writing—review & editing), Pablo Garcia-Pavia (Conceptualization; Writing—review & editing), Milind Desai (Writing—review & editing), and Farbod Sedaghat-Hamedani (Visualization; Writing—original draft; Writing—review & editing)

Declarations

Disclosure of Interest

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Data Availability

No new data were generated or analysed in this study. Data sharing is therefore not applicable.

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