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Review Article

Management Strategies for Hypertrophic Cardiomyopathy – A Review

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Abstract:

Hypertrophic cardiomyopathy (HCM) is the most common genetically inherited cardiomyopathy, with a prevalence near 1 in 500. HCM manifests as the presence of left ventricular (LV)hypertrophy that cannot be explained by the hemodynamic conditions. The characteristic histological findings are myocyte disarray and fibrosis. The most common imaging findings are asymmetric hypertrophy of the interventricular septum; this is often associated with a narrowed LV outflow (LVOT) and flow acceleration at that level. Imaging techniques such as echocardiography and cardiac magnetic resonance imaging play a crucial role in the diagnosis and management of patients with HCM.

HCM can lead to myocardial ischemia, LVOT obstruction leading to exercise intolerance, heart failure (HF), and increased risk of sudden cardiac death (SCD). Management is focused on reducing the risk of SCD, limiting dynamic LVOT obstruction and progression of symptoms with lifestyle and pharmacologic modulation. HCM represents a challenging condition given the marked genetic and phenotypic heterogeneity in clinical manifestations, disease course, age of onset, pattern and extent of LV hypertrophy, degree of obstruction, and risk for sudden cardiac death.

Invasive procedures like septal myectomy and alcohol septal ablation (ASA) are indicated when non-invasive management is unsuccessful. These procedures are associated with improved quality of life and reduction in medication burden. Currently, there are no trials that have compared septal myectomy and ASA, but the European Society of Cardiology and the American College of Cardiology offers conflicting recommendations supporting ASA vs. septal myectomy, respectively.

However, both advocate multidisciplinary team discussions with careful consideration of comorbidities, frailty, and patient preferences.

This review outlines the pathophysiology and diagnosis of HCM, medical management and then focuses on invasive procedures available, evidence on outcomes, and the guidelines from different bodies governing invasive decision making.

Key words: Hypertrophic cardiomyopathy; LV outflow tract obstruction; Septal myectomy; Alcohol septal ablation; Sudden cardiac death; Heart failure; Echocardiography; Cardiac MRI; Septal reduction therapy.

Section 1: Definition, Pathophysiology, & Epidemiology

1.1 Definition

Hypertrophic cardiomyopathy (HCM) is characterized by unexplained myocardial hypertrophy in the absence of abnormal loading conditions such as hypertension or valvular disease (Elliott & McKenna, 2004; McKenna & Judge, 2021; Richardson, 1996). Hypertrophy is often asymmetric, predominantly affecting the interventricular septum (Federspiel et al., 2024). Diagnosis typically occurs in adolescence or early adulthood but may remain subclinical for years and progress variably over the lifespan (Ho et al., 2018; B. J. Maron et al., 2016).

1.2 Pathophysiology

HCM was initially described as an outflow tract obstructive disorder. While ~70% of cases have left ventricular (LV) outflow tract (LVOT) obstruction, approximately half of these cases have obstruction occurring only upon provocation (e.g., with Valsalva maneuver or exercise; Geske et al., 2009; Maron et al., 2009; Rowin, Maron, et al., 2017). Obstruction is typically dynamic and caused by systolic anterior motion (SAM) of the mitral valve (Nordenstrom & Ovenfors, 1962). Diastolic dysfunction is a key feature, elevating left ventricle end-diastolic pressure (LVEDP) and causing pulmonary congestion which leads to symptoms (Fifer & Vlahakes, 2008; B. J. Maron & Maron, 2013). Myocyte disarray and interstitial fibrosis impair conduction and contraction, predisposing to ventricular arrhythmias and sudden cardiac death (SCD; O'Mahony et al., 2014; Santini et al., 2021).

1.3 Epidemiology

HCM affects greater than 1 in 500 individuals, with higher diagnosis rates in young males and elderly females (Elliott & McKenna, 2004; Semsarian et al., 2015). HCM may be more prevalent among Black Americans (B. J. Maron et al., 1995). Prevalence may be overestimated in highly screened populations (e.g., athletes, military recruits) due to physiological or hypertensive left ventricular hypertrophy (LVH; McKenna & Judge, 2021). Pediatric prevalence is lower (0.3-0.5 per 100,000), peaking in infants <1 year with a male predominance (1.7:1) (Lipshultz et al., 2003; Nugent et al., 2003).

1.4 Genetics

Between 50-60% of HCM cases involve autosomal dominant sarcomere mutations (e.g., MYH7, MYBPC3) with variable expressivity and incomplete penetrance (Marian & Braunwald, 2017; McKenna & Judge, 2021; Rowin et al., 2020). Genotype-phenotype correlations are weak, but pathogenic variants without structural disease are rare and should be interpreted cautiously (Marian, 2014; McKenna & Judge, 2021).

1.4 Phenocopies

HCM is primarily caused by sarcomeric gene mutations. Non-sarcomeric causes include metabolic (e.g., Pompe, Danon, Fabry), syndromic (e.g., Noonan's, LEOPARD), neuromuscular (e.g., mitochondrial myopathies), other gene mutations (e.g., muscle LIM protein), and other causes like obesity, athletic training, or amyloidosis. In pediatric populations, congenital, metabolic, or neuromuscular etiologies dominate while in adolescents and adults familial and sarcomeric mutations are most common (Elliott & McKenna, 2004; Geier et al., 2003; Lipshultz et al., 2003; Nugent et al., 2003).

1.5 Natural History

Many patients remain asymptomatic or experience mild symptoms. Approximately 40% develop progressive heart failure, particularly with resting LVOT obstruction (B. J. Maron et al., 2016; Rowin, Hausvater, et al., 2017; Rowin, Maron, et al., 2017). Atrial fibrillation (AF), predominantly paroxysmal, occurs in 17-20% (Rowin, Hausvater, et al., 2017; Rowin, Maron, et al., 2017). Five percent experience SCD and among young athletes it accounts for more than a third of deaths (B. J. Maron et al., 2009; Rowin, Maron, et al., 2017). Advances in treatment mostly with implantable defibrillators have reduced HCM-attributable annual mortality to roughly 0.5%, with overall mortality around 1% (Geske et al., 2018; B. J. Maron, 2018).

Section 2: Diagnostics

Despite a prevalence of 1 in 500, HCM remains underdiagnosed due to its heterogeneous and overlapping presentations, with confirmed diagnoses occurring in only 1 in 3000 (Gersh et al., 2011). Recognizing its clinical features and applying appropriate diagnostic criteria are essential for timely management.

2.1 History

HCM often presents with non-specific, exertional symptoms such as dyspnea, angina, dizziness, or syncope (Fifer & Vlahakes, 2008). Symptom severity ranges from mild limitation to more severe including resuscitated SCD and can fluctuate daily depending on hemodynamic conditions (Fifer & Vlahakes, 2008; Wigle, 2001).

2.2 Physical Exam

Examination may reveal a forceful, sustained apical impulse, S4, and a harsh crescendo decrescendo systolic ejection murmur (SEM) at the apex. Obstructive HCM may present with a louder SEM during Valsalva and/or a double or triple apical impulse in the left lateral decubitus position. With right ventricular involvement, a prominent A-wave in the JVP and/or SEM at the left upper sternal border may also be observed (Wigle, 2001).

2.3 Electrocardiogram

Electrocardiogram (ECG) abnormalities are seen in ~95% of HCM patients, supporting its use as a screening tool (McLeod et al., 2009). Findings include signs of LVH, ST-T abnormalities, repolarization abnormalities (secondary to the histological changes), pathological Q waves, atrial enlargement, and conduction delays (Bernardini et al., 2023). Abnormal ECGs warrant further imaging with echocardiography or cardiac MRI. In apical variant HCM, ECG changes are often more pronounced than abnormalities visible by echocardiography (Figure 1).

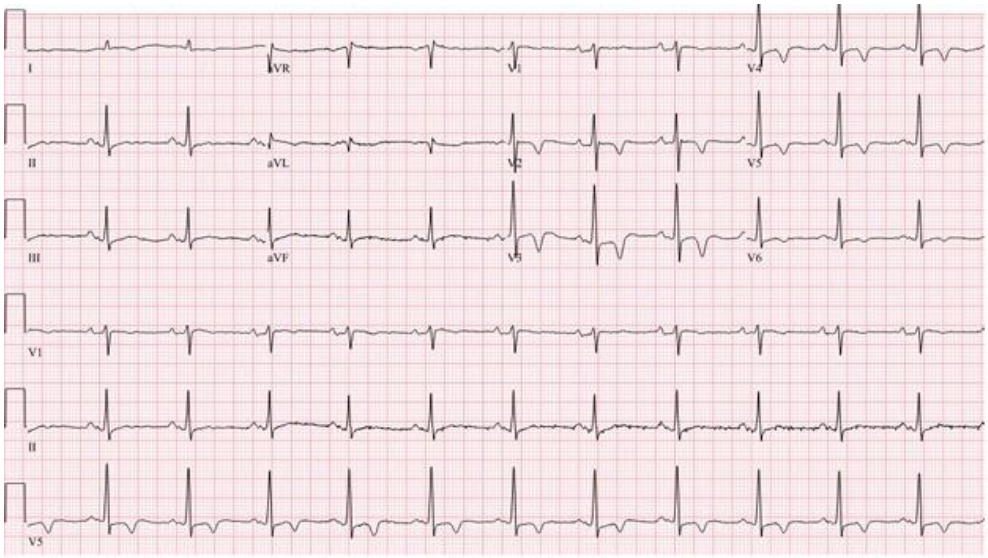

Figure 1: ECG of a patient with apical HCM showing LVH and markedly negative T waves in the anterior leads.

2.4 Echocardiography

Transthoracic echocardiography (TTE) is the first-line diagnostic modality for HCM, defined by unexplained end-diastolic LV wall thickness ≥ 15 mm in one or more myocardial segments (or ≥ 13 mm in subjects with a family history), with 13-14 mm considered borderline in the presence of suggestive features (Elliott et al., 2007; Gersh et al., 2011; Richardson, 1996). Echocardiography also characterizes the phenotypic expression of HCM, including asymmetric septal hypertrophy, apical HCM, and mid-ventricular obstruction, each of which carries distinct hemodynamic and clinical implications (Parato et al., 2015). In addition to assessing LVOT gradients and SAM of the mitral valve, echocardiography provides critical evaluation of diastolic dysfunction, a major contributor to symptoms even in the absence of significant LVOT obstruction (Haland & Edvardsen, 2020).

LVOT gradients can also be characterized on TTE, with nearly 30% of HCM patients having a resting gradient and another 30-40% demonstrating a provokable gradient with Valsalva, pharmacologic maneuvers, or exertion. A gradient > 30 mmHg is considered significant. Mitral valve (MV) regurgitation is also common and can be due to SAM or anatomical abnormalities of the leaflets or subvalvular apparatus. Characterization of such abnormalities is crucial in guiding intervention.

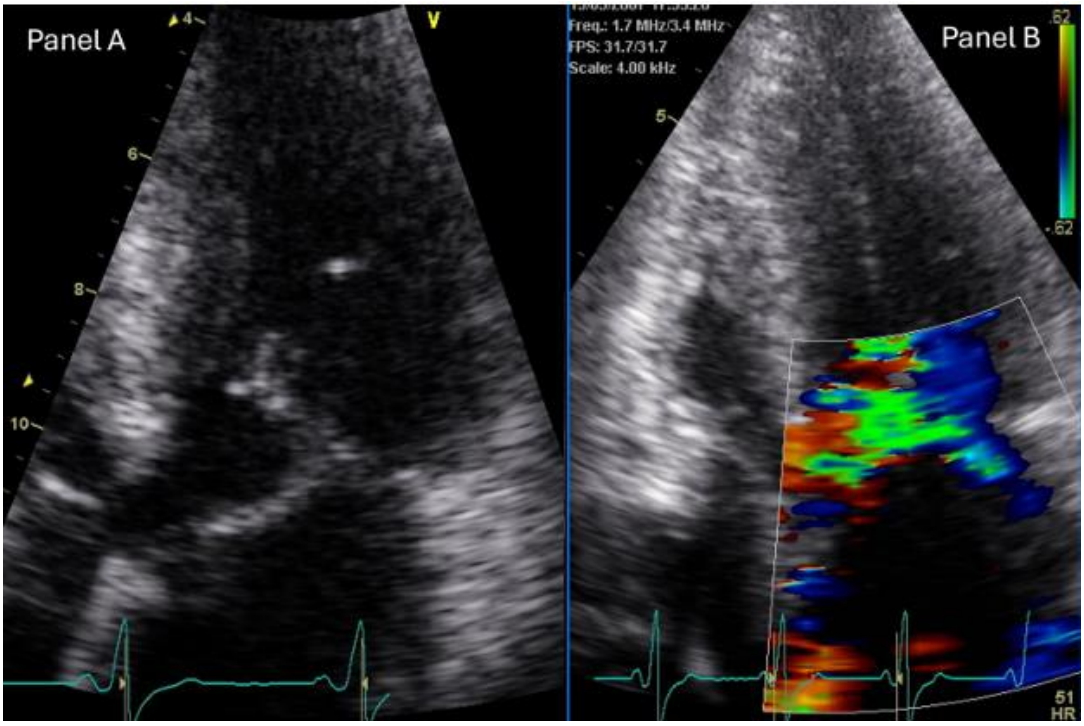

Figure 2: Echocardiogram of a patient with obstructive hypertrophic cardiomyopathy. Panel A: Two-dimensional imaging apical 4 chamber view showing asymmetric predominantly septal left ventricular hypertrophy with systolic anterior motion of the mitral valve leaflets. Panel B: color imaging showing left ventricular outflow tract obstruction at mid systole and posteriorly directed mitral regurgitation.

2.5 Cardiac MRI

Cardiac MRI (CMR) is used when echocardiography is inconclusive or borderline, providing superior accuracy for wall thickness measurements, particularly in the posterolateral wall (Corona Villalobos et al., 2016). CMR also enables tissue characterization through late gadolinium enhancement (LGE), which can detect myocardial fibrosis to aid risk stratification as extent of LGE is associated with SCD risk (Meier et al., 2024).

2.6 Genetic Testing

In 60% of HCM cases, sarcomeric gene panels (e.g., MYH7, MYBPC3, TNNT2, TNNI3) identify a pathogenic variant (Bonaventura et al., 2021); however, many causative mutations remain undiscovered, and a negative result does not exclude disease (Marian & Roberts, 2001; Seidman & Seidman, 2001). In the presence of a pathogenic mutation, cascade screening is offered to first degree relatives of affected individuals (Bonaventura et al., 2021).

2.7 Histology

Autopsy or myocardial biopsy can demonstrate histological features like myocyte disarray, interstitial fibrosis, and small vessel disease, but these are highly non-specific and biopsy is not

generally indicated (Elliott & McKenna, 2004).

2.8 Risk Stratification

SCD risk should be assessed at time of HCM diagnosis (Gersh et al., 2011). The European Society of Cardiology score for SCD (ESC HCM Risk-SCD model) calculates 5-year risk based on septal thickness, left atrium diameter, LVOT gradient, non-sustained ventricular tachycardia, and family history (O'Mahony et al., 2014). Similarly, the ACCF/AHA guidelines use categorical risk markers to guide decision-making about implantable cardioverter-defibrillator (Gersh et al., 2011).

2.9 Differential Diagnoses

The differential diagnosis for HCM includes hypertensive heart disease, athlete's heart (physiological LV hypertrophy resolving with deconditioning), and HCM phenocopies (Chetrit et al., 2022). Treating comorbid hypertension and reassessing for regression of hypertrophy, along with clinical, imaging, and biomarker findings can aid diagnostic clarification (McKenna & Judge, 2021). Differential diagnoses are beyond the scope of this review and can be reviewed at other dedicated resources (e.g., Yilmaz & Sechtem, 2014).

Section 3: Non-Invasive Management

3.1 Lifestyle

3.1.1 Physical Activity and Competitive Sports

While initial concerns around physical activity stemmed from its association with SCD in young athletes, later research showed that most SCD events in HCM occur independent of exercise (Corrado et al., 2004; Finocchiaro et al., 2017; Heitner & Fischer, 2019; Lampert et al., 2023; Maki et al., 1998; B. J. Maron et al., 2009; Sweeting et al., 2016). Given the cardioprotective benefits of exercise, the American Heart Association now recommends mild-to-moderate intensity exercise (Class I; Ommen et al., 2024). Universal restriction from vigorous recreational activities or competitive sports is not indicated, provided that an annual comprehensive evaluation is performed by an expert (Lampert et al., 2023; Ommen et al., 2024). Activities like cycling, modest hiking, lap swimming, treadmill use, golf, or skating are encouraged, while high-intensity activities (ex. basketball, soccer, sprinting) or those that carry risk for sudden loss of consciousness (ex. scuba diving, weightlifting) require close review by the cardiologist (Ommen et al., 2024). Genotype-positive but phenotype-negative patients have no restrictions, recognizing that structural disease is the primary driver for arrythmia risk (Ommen et al., 2024; Semsarian et al., 2015).

3.1.2 Dietary and Fluid Management

The dynamic nature of LVOT obstruction is highly sensitive to changes in preload or afterload, and dehydration reduces LV end-diastolic volume, narrowing the tract and increasing flow velocity which exacerbates SAM (Fifer & Vlahakes, 2008; Heitner and Fischer, 2019). Maintaining adequate hydration is essential to preserve preload and minimize symptoms (Finocchiaro et al., 2017; as cited in Heitner & Fischer, 2019). Dietary factors also play a role, with many reporting exacerbations after large, carbohydrate-rich meals or drinking alcohol (Paz et al., 1996; as cited in Heitner & Fischer, 2019). It is therefore recommended to eat smaller meals with fewer simple carbohydrates and more complex carbohydrates (e.g., whole grains, vegetables, oats). Alcohol consumption is discouraged as it contributes to peripheral vasodilation and potential dehydration (Heitner & Fischer, 2019).

3.1.3 Pregnancy

Pregnancy is generally well-tolerated in HCM, but carries some risks due to increased blood volume, cardiac demand, and the pro-arrhythmic nature of pregnancy (Saberi, 2021). However, the decree of LVOT obstruction often decreases in pregnancy, so this risk is not typically prohibitive and management includes anticoagulation with low-molecular weight heparin or low dose warfarin for those with AF and beta-blockers if symptomatic (Regitz-Zagrosek et al., 2018). Counselling against pregnancy is only indicated for a small group of patients with severe preconception disease (Saberi, 2021). Vaginal delivery is first line (class I; Regitz-Zagrosek et al., 2018). Cardioversion for AF and serial ECG monitoring is also reasonable, especially if the patient is symptomatic (class IIa; Regitz-Zagrosek et al., 2018).

3.2 Pharmacological Therapy

Pharmacological therapy is indicated for symptomatic HCM, particularly in those experiencing exercise intolerance or angina from mechanical resistance in the LVOT (Fifer & Vlahakes, 2008; Maron et al., 2022). Current management focuses on reducing the inotropic state to minimize the hydrodynamic drag that initiates SAM of the MV, lowering the LVOT gradient and improving cardiac efficiency (Karaarslan et al., 2024; B. J. Maron, Dearani, et al., 2022). Treatment must be tailored to both the hemodynamic subtype (obstructive versus non-obstructive) and the presence of concurrent conditions such as atrial fibrillation (AF) or reduced ejection fraction. The management paradigm for SCD prevention, discussed earlier, emphasizes continuous risk stratification for ICD placement (Ommen et al., 2024; Santini et al., 2021). Asymptomatic patients with no concurrent conditions and minimal SCD risk are otherwise managed with lifestyle modifications and observation as discussed above. Persisting symptoms after maximal pharmacotherapy is an indication for invasive management (B. J. Maron, Dearani, et al., 2022; Nishimura & Holmes, 2004). The initial pharmacological management of symptomatic HCM focuses on non-vasodilating negative inotropic and

negative chronotropic agents (B. J. Maron, Desai, et al., 2022; Ommen et al., 2024). The therapeutic goal is the improvement of the patient's functional status rather than the abolition of the gradient at rest (Ommen et al., 2024).

3.2.1 Beta-Adrenergic Blocking Agents

Beta-blockers (BBs) remain the foundational first-line therapy for most symptomatic HCM cases (B. J. Maron, Desai, et al., 2022; Smith et al., 2025). Slowing the heart rate prolongs diastole, increasing end-diastolic volume and producing a more favorable geometry that keeps the mitral valve further from the septum (Karaarslan et al., 2024; Smith et al., 2025). Vasodilating betablockers like carvedilol and labetalol, however, must be avoided in obstructive HCM as the reduction in afterload can paradoxically increase the LVOT gradient (Ommen et al., 2024). BB therapy should be titrated to a target heart rate of 50-60 beats per minute and until symptomatic benefit is observed (Ommen et al., 2024; Smith et al., 2025). A trial of beta-blockade should not be declared a failure until there is demonstrated physiologic evidence of blockade, such as the suppression of resting heart rate (Ommen et al., 2024).

3.2.2 Disopyramide

Disopyramide is a class 1a antiarrhythmic utilized as second-line treatment for refractory obstructive HCM (Massera et al., 2025). Its potent negative inotropic properties slow the rate of LV pressure rise and decrease early systolic blood flow velocity, reducing the hydrodynamic "drag" that pulls the MV into the septum (Karaarslan et al., 2024; Massera et al., 2025). Disopyramide must be used in combination with an atrioventricular nodal blocking agent to prevent rapid ventricular conduction in the event of AF (Massera et al., 2025; Ommen et al., 2024). Systemic anticholinergic side effects can be mitigated by adjunctive pyridostigmine, allowing higher doses to be utilized (Massera et al., 2025; Teichman et al., 1985).

3.2.3 Targeted Molecular Therapy: Cardiac Myosin Inhibitors

The introduction of cardiac myosin inhibitors (CMIs) represents a paradigm shift toward precision molecular therapy. CMIs are the first disease-targeted therapy in HCM, directly reducing actinmyosin cross-bridge formations and shifting myosin heads toward an energy-sparing, 'off-actin' state, thereby attenuating hypercontractility at its molecular origin (B. J. Maron, Desai, et al., 2022; Wilcox & McNally, 2020). Mavacamten and Aficamten are the only two CMIs currently approved.

3.2.3.1 Cardiac Myosin Inhibitors in Obstructive HCM

Both approved CMIs, Mavacamten and Aficamten, are currently indicated for the treatment of symptomatic obstructive HCM (oHCM; resting or provoked peak gradient ≥ 30 mmHg) in adults with LVEF ≥55% (Mavacamten) or ≥60% (Aficamten) and NYHA class II-III symptoms. The 2024 AHA/ACC guideline assigns CMIs a Class I recommendation as second-line therapy for oHCM (M. S. Maron et al., 2024; Olivotto et al., 2020; Ommen et al., 2024). Phase 3 trials establish CMIs as effective in HCM. EXPLORER-HCM showed Mavacamten improves functional capacity, including an improved pVO2, NYHA functional class, and quality of life, as well as reduced postexercise LVOT gradient (Olivotto et al., 2020). VALOR-HCM demonstrated that Mavacamten reduced eligibility for septal reduction therapy (SRT) in patients referred for SRT at 16 weeks with sustained improvements at 128 weeks. While LVEF declined below 50% in 13.9% of patients over that period, all were managed by dose adjustment without drug discontinuation (Desai et al., 2022; Desai, Owens, et al., 2025). More recently, Mavacamten was found to be effective in reducing LVOT gradients in adolescents aged 12-17 years without increased adverse reactions (Rossano et al., 2026). SEQUIA-HCM subsequently established Aficamten's efficacy in oHCM through improved pVO2 compared to placebo as well as each of the other pre-specified secondary endpoints including NYHA class, Valsalva LVOT gradient, and quality of life measures with no instances of LVEF falling below 50% in the trial period (M. S. Maron et al., 2024). MAPLE-HCM Aficamten monotherapy demonstrated superiority over metoprolol across all clinically relevant efficacy endpoints at 24 weeks, being the first head-to-head comparison of CMIs and beta-blockers, the longstanding definitive first-line therapy for oHCM (Garcia-Pavia et al., 2025).

The long-term implications of sustained myosin inhibition on cardiac structure and arrhythmic burden require ongoing surveillance, and these drugs are not without risk in selected patients, but continued research is likely to influence future guideline revisions (Desai, Wolski, et al., 2025; B. J. Maron, Desai, et al., 2022).

3.2.3.1 Cardiac Myosin Inhibitors in Non-Obstructive HCM

Neither Mavacamten nor Aficamten is currently approved for non-obstructive HCM (nHCM; resting or provoked peak gradient < 30 mmHg) and the CMI evidence base is limited. The phase 2 MAVERICK-HCM trials demonstrated significant reductions in NT-proBNP and cardiac troponin versus placebo, but failed to achieve the primary functional endpoints of improved pVO2 or NYHA class. Notably, 12.5% of patients in the active treatment groups experienced reversible LVEF reductions to ≤45%, highlighting a disproportionate safety concern in the absence of LVOT obstruction which may otherwise buffer against excessive systolic depression (Wilcox & McNally, 2020). The subsequent phase 3 ODYSSEY-HCM trial, the largest and longest study in nHCM to date, evaluated Mavacamten over 48 weeks against placebo using co-primary endpoints of change in pVO_2 and KCCQ-23 Clinical Summary Score and did not meet either primary endpoint. Although exploratory secondary analyses showed directional improvements in cardiac biomarkers, LV diastolic indices, and left atrial remodeling with Mavacamten, these did not translate into clinically meaningful gains in symptoms or exercise capacity in the overall population. Reversible LV systolic dysfunction occurred in approximately one in five patients (Desai, Owens, et al., 2025). These findings emphasize that nHCM and oHCM are pathophysiologic ally distinct, and that pharmacological targets effective in the obstructive phenotype do not translate directly. Whether earlier treatment, more refined patient selection by biomarker profile, diastolic dysfunction severity, or more sensitive endpoints could identify a responsive nHCM subgroup remains an open question. The ongoing phase 3 ACACIA-HCM trial is evaluating aficamten specifically in nHCM and will provide further insight (M. S. Maron et al., 2024).

3.2.3.3 Drug Interactions and Safety Considerations

Mavacamten is a CYP2C19 and CYP3A4 substrate; use with moderate-to-strong CYP inhibitors or inducers requires dose adjustment or is contra-indicated. The drug is teratogenic and subject to a US-mandated Risk Evaluation and Mitigation Strategy programme requiring prescriber enrolment and mandatory echocardiographic surveillance. Concurrent use of Mavacamten and disopyramide is not routinely recommended outside specialist centres due to additive negative inotropic effects. For both

approved CMIs, structured echocardiographic monitoring is essential (Table 1).

Agent	InitiationThreshold	Monitoring Schedule	Safety Action
Mavacamten	LVEF ≥ 55%	• Weeks 4, 8, 12 • 4 weeks post-dose change • Every 6 months when stable (LVEF ≥ 55%, gradient < 30mmHg) (Scholtz et al., 2023a)	• Interrupt if LVEF <50% • Repeat TTE at 4weeks • Restart at lower dose after LVEF recovery
Aficamten	LVEF ≥ 60%	• Titration visits at weeks 2, 4,6 per SEQUIOA-HCMprotocol • Post-marketing schedules prescribing information (Maron et al., 2024)	Post-marketing data required, no LVEF < 50% events in SEQUIOA-HCM and one event in MAPLE-HCM

Table 1: Echocardiographic Monitoring Framework for Cardiac Myosin Inhibitors.

LVEF = Left Ventricular Ejection Fraction; LVOT = Left Ventricular Outflow Tract; TTE = Transthoracic Echocardiography

3.2.4 Algorithmic Approach to Pharmacological Management

An algorithmic pharmacological framework, stratified by HCM subtype and escalating along lines of first-, second-, and third-line therapy, is presented below for oHCM (Table 1) and nHCM (Table 2), integrating 2024 AHA/ACC guideline recommendations with the current evidence base (Ommen et al., 2024).

Line	Agent(s)	Key Considerations
First	Non-vasodilating beta-blocker (e.g., metoprolol, propranolol, atenolol) OR Non-DHP CCB (verapamil, diltiazem) if BB not tolerated/contraindicated	• Titrate to resting HR ~60-65 bpm. • Combination of BB + CCB unsupported. • Verapamil contraindicated if hypotension, severe dyspnea at rest, or LVOT gradient >100 mmHg. • Monitor heart rate, BP, LVOT gradient and clinical changes (Ommen et al., 2024).
Second	Cardiac myosin inhibitor (Mavacamten or Aficamten, in adults only) OR Disopyramide (always with AV nodal blocker)	• CMI: Requires LVEF ≥55% (Mavacamten) or ≥60% (Aficamten); mandatory echocardiographic monitoring; teratogenic. • Disopyramide: QTc and echo monitoring; anticholinergic side effects common; contraindicated if LVEF
Third	Invasive septal reduction therapy (septal myectomy preferred at experienced centres, or alcohol septal ablation where surgery contraindicated)	Indicated when maximally tolerated GDMT fails to adequately control symptoms. All three major society guidelines (AHA/ACC, ESC, CCS) concur that SRT should only follow failure of optimized pharmacological therapy (Ommen et al., 2024).

Table 2: Algorithmic Pharmacological Management of Obstructive HCM BB = Beta-Blocker; BP = Blood Pressure; CCB = Calcium Channel Blocker; CMI = Cardiac Myosin Inhibitor; DHP = Dihydropyridine; LVOT = Left Ventricular Outflow Tract; QTc = Corrected QT Interval

Line	Agent(s)	Key Considerations
First	Beta-blocker OR non-DHP CCB (verapamil/diltiazem)	• Preserved EF: target exertional dyspnoea and angina. • Add oral diuretics if exertional dyspnoea persists. • No proven disease-modifying pharmacotherapy currently exists for nHCM (Ommen et al., 2024).
Second	Diuretics for congestion. For EF	• Narrow preload range in nHCM, diuretics must be titrated carefully. • Vasodilators, DHP-CCBs, and digoxin should be avoided in obstructive forms. • Disopyramide, vasodilators, and CMIs are not approved/recommended in nHCM at present (Ommen et al., 2024).
Third	Aficamten (ACACIA-HCM ongoing);	Mavacamten did not significantly improve pVO_2 or KCCQ-CSS versus placebo in nHCM at 48 weeks in ODYSSEY-HCM. ACACIA-HCM will determine whether

	Mavacamten (ODYSSEY-HCM completed, primary endpoints not met)	Aficamten can extend CMI benefit to nHCM. Neither drug is currently approved for nHCM (Desai, Owens, et al., 2025; M. S. Maron et al., 2024).

Table 3: Algorithmic Pharmacological Management of Non-Obstructive HCM

CCB = Calcium Channel Blocker; CMI = Cardiac Myosin Inhibitor; DHP = Dihydropyridine; EF= Ejection Fraction; GDMT = Goal-Directed Medical Therapy; HFrEF = Heart Failure wit Reduced Ejection Fraction; nHCM = Non-Obstructive HCM

3.2.5 Management of Secondary Manifestations and Complications

One-quarter of HCM cases also present with atrial fibrillation due to the associated left atrial dilatation (Weissler-Snir et al., 2024). AF detection in HCM patients warrants lifelong oral anticoagulation regardless of the CHA2DS2-VASc score, with direct oral anticoagulants as the preferred agents (Ammirati et al., 2016; Ommen et al., 2024). Management of AF symptoms focuses on rate control with BBs or CCBs and rhythm control to maintain the atrial contribution to ventricular filling (Ommen et al., 2024; Rowin, Hausvater, et al., 2017). Patients who progress to systolic dysfunction (LVEF < 50%), often termed the "burnt-out" phase, require guideline-directed medical therapy (GDMT) for heart failure, including ACE inhibitors, ARBs, and SGLT2 inhibitors (Mapelli et al., 2025; B. J. Maron, Desai, et al., 2022). Medications like amiodarone or nadolol may be considered for those with prior ventricular arrythmias (Ammirati et al., 2016).

3.2.6 Summary of Section

The emergence of CMIs represents a paradigm shift in HCM pharmacotherapy. EXPLORER HCM and SEQUOIA-HCM provide the most rigorous evidence yet in oHCM drug development, demonstrating consistent and clinically meaningful improvements in exercise capacity, LVOT obstruction, symptoms, and quality of life. VALOR-HCM further establishes mavacamten's capacity to reduce SRT eligibility over extended periods in severely symptomatic patients. MAPLE-HCM, published in 2025, provides the first head-to-head evidence of CMI monotherapy superiority over beta-blocker monotherapy in oHCM, with Aficamten demonstrating significantly greater improvements compared to metoprolol across all prespecified efficacy endpoints. Evidence in nHCM is currently limited and does not demonstrate translation of the same benefits as oHCM, with a higher demonstrated risk of reversible LV dysfunction in both MAVERICK-HCM and ODYSSEY-HCM trials. The upcoming ACACIA-HCM trial will determine whether CMI benefit can be translated to nHCM.

Section 4: Invasive Management

4.1 Indications for Septal Reduction Therapy

When obstructive symptoms are still not relieved by maximally tolerated GDMT as outlined above, the American, European, and Canadian guidelines all indicate invasive septal reduction therapy (SRT) (Table 4; Arbelo et al., 2023; Crean et al., 2024; Ommen et al., 2024). SRT aims to directly reduce the septal thickness to reduce LVOT obstruction and mitral-septal contact, relieving symptoms and improving quality of life and exercise tolerance (Nishimura & Ommen, 2010). Currently, two approved SRT methods exist – surgical septal myectomy (SM) and trans-catheter alcohol septal ablation (ASA).

Recommendations	**Class**	**Level**
2024 AHA/ACC/AMSSM/HRS/PACES/SCMR Guideline for the Management of Hypertrophic Cardiomyopathy		
In patients with obstructive HCM who remain symptomatic despite GDMT, SRT in eligible patients performed at experienced HCM centres is recommended for relieving LVOTO.	1	**B**
For symptomatic patients with obstructive HCM, SRT in eligible patients performed at experienced HCM centres may be considered as an alternative to escalation of medical therapy after shared decision-making including risks and benefits of all treatment options.	2b	C
For patients with HCM who are asymptomatic and have normal exercise capacity, SRT is not recommended.	3	C
2023 ESC Guidelines for the management of cardiomyopathies		
SRT to improve symptoms is recommended in patients with a resting or maximum provoked LVOT gradient of ≥50 mmHg who are in NYHA/Ross functional class III-IV, despite maximum tolerated medical therapy.	1	B
SRT should be considered in patients with recurrent exertional syncope caused by a resting or maximum provoked LVOTO gradient ≥50 mmHg despite optimal medical therapy.	2a	C
SRT may be considered in expert centres with demonstrable low procedural complication rates in patients with mild symptoms (NYHA class II) refractory to medical therapy who have a resting or maximally provoked (exercise or Valsalva) gradient of ≥50 mmHg and: • Moderate-to-severe SAM-related mitral regurgitation; or • AF; or • Moderate-to-severe left atrial dilatation.	2b	C

Table 4: American and European guidelines governing the indications for SRT in patients with HCM (Arbelo et al., 2023; Ommen et al., 2024).

4.2 Septal Myectomy

Septal myectomy (SM) is the gold-standard surgical therapy for oHCM, first described by Dr. Andrew Glenn Morrow in the 1960s (Goodwin et al., 1960; Karaarslan et al., 2024; B. J. Maron, Dearani, et al., 2022; B. J. Maron & Roberts, 2016; Morrow et al., 1968; Pelliccia et al., 2021). The classical Morrow procedure involves a transaortic approach to resect a small, well-defined mass from the hypertrophied septum extending

proximally from the basal septum below the aortic valve to the point of the mitral-septal contact distally (Karaarslan et al., 2024; Morrow et al., 1968; Pelliccia et al., 2021). This widens the LVOT, producing immediate relief of the obstruction and MR and significant improvements in symptoms (Karaarslan et al., 2024; B. J. Maron, Dearani, et al., 2022; B. J. Maron & Roberts, 2016; Morrow et al., 1968; Pelliccia et al., 2021). The modified Morrow procedure, first described by Dr. Bruno Messmer is now widely adopted. The muscularexcision is longer and wider, from below the aortic annulus proximally to the level of the papillary muscles distally, beyond the area of mitral-septal contact (B. J. Maron, Dearani, et al., 2022; Messmer, 1994). This avoids any residual midventricular obstruction and improves SAM by mobilizing the papillary muscles (B. J. Maron, Dearani, et al., 2022; Messmer, 1994; Pelliccia et al., 2021).

Contemporary techniques address abnormal anatomical features such as aberrant mitral valve or papillary muscle structures. Mitral valve replacement (MVR) was previously recommended for all SM patients to definitively address SAM and mitral-septal leaflet contact, but growing evidence of risks means replacement is now only indicated in unresolvable pathology or when the basal septal thickness is mild (<18 mm) and the mitral pathology is the main contributor to LVOT obstruction (B. J. Maron, Dearani, et al., 2022). The evidence on concurrent MV repair to address abnormal valve pathology (e.g. elongated leaflets) is still inconclusive and thus, rates of concomitant mitral valve repair differ largely by center and surgeon preference. Subvalvular intervention is common during SM, including resection of abnormal papillary muscles or excision of any fibrous tissue connecting the MV leaflets to the LV free wall, septum, or the papillary muscles (B. J. Maron, Dearani, et al., 2022). For patients with paroxysmal or sustained AF, conjunctive operative ablation via the Cox Maze IV procedure can be performed with one center showing a rate of 55% free from AF at 8year follow-up (B. J. Maron, Dearani, et al., 2022).

Apical hypertrophy is better addressed by a trans-apical approach (Afanasyev et al., 2024; Hughes et al., 2020; Li et al., 2024). Rather than SAM of the mitral valve and LVOT obstruction, this variant causes LV cavity obliteration during systole leading to symptoms from midventricular obstruction and diastolic dysfunction (Hughes et al., 2020; Li et al., 2024). Additionally, 20-30% develop an apical aneurysm, increasing SCD risk. An apical ventriculotomy is performed laterally from the left anterior descending artery and ventricular septal myectomy and shaving and shaving of the anterolateral and posterior free walls is performed (Afanasyev et al., 2024; Li et al., 2024). If there is also mid-ventricular obstruction not accessible through the apical access, a combined transaortic-transapical approach can be performed (Hughes et al., 2020; Li et al., 2024; B. J. Maron, Dearani, et al., 2022; Tuohy et al., 2020).

Post-operative complications following SM are relatively rare and include conduction disease, most commonly a left bundle branch block. As such, a temporary pacemaker should be implanted pre-operatively in those with pre-existing right bundle branch block. Other complications or limitations include regular contraindications to open heart surgery, the development of interventricular communications in rare cases, or new-onset aortic valve insufficiency (likely due to valve injury; Antunes & Scudeler, 2020; Juarez-Casso et al., 2024; Raheja et al., 2022). Intra-operative or post-operative repair of the interventricular communications and aortic insufficiency is often needed, and unique techniques have been described in the literature (Raheja et al., 2022).

4.3 Alcohol Septal Ablation

Alcohol septal ablation (ASA) was first developed as an alternative to SM in 1995 by Dr. Ulrich Sigwart (Scholtz et al., 2023b; Sigwart, 1995; Veselka, 2024). Brugada et al. had only recently applied the injection of alcohol into the coronaries to induce ischemic scarring for treatment of refractory ventricular tachycardia, and this was adapted by Dr. Sigwart to resolve the obstruction via necrosis and fibrosis of the septum (Fifer & Sigwart, 2011; Scholtz et al., 2023b; Sigwart, 1995; Veselka, 2024).

ASA can be performed with femoral or radial access and transesophageal or transthoracic echocardiography is used for monitoring (Fifer & Sigwart, 2011; Scholtz et al., 2023b). The first septal perforator is identified via coronary angiogram (possibly aided by pre-operative CT coronary angiography) and engaged with a balloon catheter, which is inflated at a low pressure to occlude the artery. Some centres use myocardial contrast echocardiography (MCE), where an echocardiographic contrast can be injected into the first septal at this stage, highlighting the septal territory. Displacement into papillary muscle, right ventricular free wall, LV apex, or the lateral free wall means a new perforator must be selected. If none can be identified, the procedure must be aborted at this stage (Fifer & Sigwart, 2011; Scholtz et al., 2023b; Veselka, 2024).

After identification of a suitable perforator, 95% ethanol is slowly infused through the inflated balloon catheter. The balloon remains inflated for another 10 minutes, while the LVOT gradient is measured. The goal is an LVOT gradient <50% of the pre-operative gradient, or less than 10 mmHg at rest for patients with resting gradients. If this cannot be achieved, alcohol infusion into subbranches or multiple septals may be required. Finally, an angiogram can be performed to confirm occlusion of the target septal(s) and a patent LDA. Myocardial necrosis in the chosen territory leads to a marked reduction in the LVOT gradient immediately post-procedure (Fifer & Sigwart, 2011; Scholtz et al., 2023b; Veselka, 2024). The gradient may return in the initial days post-procedure due to edema from the infarction but gradually declines to the immediate post procedure level over the next few weeks (Fifer & Sigwart,

2011; Veselka, 2024). Long-term benefits are then established via gradual thinning of the septum due to ischemia and fibrotic remodeling, improving LVOT diameter (Fifer & Sigwart, 2011; Pelliccia et al., 2021; Veselka, 2024).

As proximal septal perforators also supply the conduction system, transient post-ASA atrioventricular block (AVB) is common with 10-17% of patients developing a sustained block requiring a permanent pacemaker (PPM) (Agarwal et al., 2010; Fifer & Sigwart, 2011; Fortier et l., 2024; Pelliccia et al., 2021; Scholtz et al., 2023b; Veselka, 2024; Yokoyama et al., 2023). As such, all patients without a pre-existing PPM or ICD must have a temporary pacemaker inserted pre-operatively.

ASA also relies on septal perforator anatomy, where unfavourable anatomy or severe coronary artery disease can lead to insufficient septal occlusion, and is unable to address mitral valve pathology, potentially contributing to continuation of HF symptoms (Fortier et al., 2024).

4.4 Septal Myectomy Versus Alcohol Septal Ablation – the Evidence

Most of the evidence comparing SM and ASA comes from observational studies, with no randomized control trials on the topic due to the immense sample sizes necessary from power calculations (Olivotto et al., 2007). However, large observational cohorts exist for both procedures, allowing comparisons.

While initial SM post-operative mortality rates were high at 8%, technique improvement has shown positive outcomes with rates now closer to 1% (and 3-4% with concomitant MV repair), lower than

coronary artery bypass grafting (CABG; 3%) and valve replacement (3%) (Antunes & Scudeler, 2020; B. J. Maron, Dearani, et al., 2022). Long-term survival post-SM is indistinguishable from a general population over 1, 5, and 10-years post-op. SM reverses HF symptoms for patients, with 90% of procedures abolishing the obstruction and MR, improving LV filling and function (Antunes & Scudeler, 2020). LVOT gradients are reduced from ≥50 mmHg pre-op to negligible levels (<10 mmHg) post-op. SM is effective across the whole septal thickness range, from ≤15 mm (mild) to ≥30 mm (massive) (B. J. Maron, Dearani, et al., 2022). ASA has

also demonstrated consistent, positive outcomes through analyses of large cohorts like the EuroASA registry, showing a 1% thirty-day mortality, 77% 10-year survival, and a significant reduction in LVOT gradient and NYHA class (Pelliccia et al., 2021; Scholtz et al., 2023b). Reduction in LVOT obstruction was associated with alcohol dose; however, CHB rates also increased with greater doses (Scholtz et al., 2023b). In the long-term, MR and LV end-diastolic pressure was significantly reduced, improving LA pressures and size, reducing pulmonary hypertension, and increasing exercise tolerance (Pelliccia et al., 2021). A 2023 systematic review and meta-analysis of 27 studies (patients: 9332 SM, 6636 ASA) by Yokoyama et al. demonstrated similar thirty-day all-cause mortality and cardiovascular mortality, stroke, and HF rehospitalizations between ASA and SM (Yokoyama et al., 2023). However, ASA had higher post-op LVOT gradients (and less reduction from pre-op gradient), long-term mortality, re-operative rate, and need for PPM (Scholtz et al., 2023b; Yokoyama et al., 2023). Outcomes are also poorer with SM following failed ASA in comparison to SM following failed SM. PPM rates after re-intervention are around 20% given pre-existing bundle branch damage from the ASA (Fortier et al., 2024; Quinata et al., 2017). Quintana et al. report increased diastolic dysfunction pre-op, cardiovascular mortality, and advanced HF, with higher interstitial and endocardial fibrosis post-ASA believed responsible (Quintana et al., 2017). It is important to consider confounders given the observational study designs; ASA is often performed on more elderly, comorbid patients that may be deemed unfit for open heart surgery. However, disparities in long-term outcomes do persist even after accounting for these differences. As such, SM is currently the gold-standard invasive HCM therapy, but careful patient selection is still necessary.

4.5 Patient Selection & Guidelines

The 2024 ACC guidelines highlight SM as the first-line therapy for obstructive HCM when performed at experienced HCM centres, with ASA to be considered in those where surgery is contraindicated or the risk outweighs the benefits in the context of comorbidities and age (Ommen et al., 2024). The European guidelines previously differed, highlighting ASA as the first-line therapy, but the most recently published guidelines similarly identify SM as the first-line, especially in children (Arbelo et al., 2023). Careful patient risk stratification and selection is necessary, however, to ensure optimal outcomes. Recommendations are summarized in Table 5.

Factors Supporting Septal Myectomy	Factors Supporting Alcohol Septal Ablation
Younger age	Older age
Fewer, less severe comorbidities	Greater comorbidities
Greater septal thickness, or septal thickness	Minimum septal thickness of 17 mm
Longer life expectancy	Shorter life expectancy
Concurrent MV, papillary muscle, or other structural abnormalities	No other structural abnormalities

Table 5: Factors favoring septal myectomy vs. alcohol septal ablation for patient selection.

Conclusion

Hypertrophic cardiomyopathy is an inherited cardiomyopathy that manifests with dynamic LVOT obstruction due to systolic anterior motion of the mitral valve and diastolic dysfunction. It remains one of the most common causes of SCD in young adults, especially athletes. Diagnostic evaluation requires thorough assessment of symptoms, functional capacity, and echocardiography, and use of cardiac MRI is helpful in further characterizing the disease. Assessment of sudden cardiac death risk with proven risk scores at time of diagnosis is crucial to guide decision-making for implantable cardioverter-defibrillator insertion. Asymptomatic patients may be managed with lifestyle modifications only, but presentation of symptoms or signs of heart failure necessitates pharmacological management with agents like beta-blockers or non-dihydropyridine calcium channel blockers, with therapy guided by the extent of obstruction. Further, CMIs are demonstrating survival benefits in those with obstructive HCM by reducing contractility and improving obstruction. Septal reduction therapy, namely septal myectomy or alcohol septal ablation, are indicated in symptomatic obstructive HCM refractory to medical management. There are no randomized control trials comparing SM and ASA; however, observational studies have shown similar morbidity and mortality with patient selection being the most crucial factor. Decision-making between SM and ASA thus requires multi-disciplinary discussion considering several factors including patient preference, age, comorbidities, life expectancy, septal thickness, and other structural anomalies within the mitral valve or papillary muscles.

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