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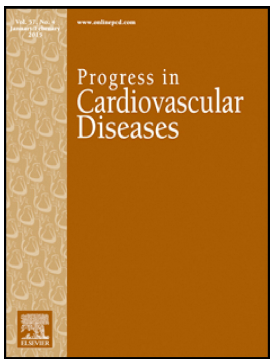

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The New Life of Myectomy in the Era of Myosin Inhibitors

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Abstract

The management of symptomatic obstructive hypertrophic cardiomyopathy remains a therapeutic clinical challenge. Surgical septal myectomy has long been established as the gold-standard intervention for patients with persistent symptoms despite optimal medical therapy, offering durable symptom relief with low perioperative risk in experienced centers.

Recently, the introduction of cardiac myosin inhibitors, such as mavacamten and aficamten, has reshaped the treatment paradigm for obstructive hypertrophic cardiomyopathy. By selectively inhibiting cardiac myosin ATPase activity, these agents reduce hypercontractility and improve myocardial energetic efficiency. Randomized, placebo-controlled trials such as EXPLORER-HCM and SEQUOIA-HCM have demonstrated the efficacy of cardiac myosin inhibitors in reducing left ventricular outflow tract gradients, alleviating symptoms, and enhancing functional capacity in patients with obstructive hypertrophic cardiomyopathy.

The growing clinical use of cardiac myosin inhibitors raises critical questions regarding their role relative to surgical intervention. While cardiac myosin inhibitors offer an effective and less invasive alternative for many patients, they do not fully replace surgical myectomy across all clinical settings.

This review articles explores the evolving therapeutic landscape of obstructive hypertrophic cardiomyopathy, focusing on the comparative advantages and limitations of cardiac myosin inhibitors and surgical myectomy.

Keywords

Myectomy, Myosin Inhibitors, obstructive hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is a genetically inherited, heterogeneous myocardial disorder primarily caused by mutations in sarcomeric protein genes, resulting in dysregulated actin-myosin cross-bridge cycling and increased calcium sensitivity, ultimately leading to myocardial hypertrophy, diastolic dysfunction, and arrhythmogenicity. Initially considered a rare and fatal condition, HCM is now recognized as relatively common, with an estimated prevalence of 1 in 500 adults. [1-3] Approximately two-thirds of patients with HCM develop left ventricular outflow tract obstruction (LVOTO), which is promoted by systolic anterior motion (SAM) of the mitral leaflets and mitral-septal contact. This kind of obstruction is dynamic and can be worsened by various physiological conditions, including exercise, the Valsalva maneuver, standing, vasodilators, or positive inotropic drugs. [4,5]

The management of symptomatic patients with obstructive hypertrophic cardiomyopathy (oHCM) has long been a clinical challenge. The initial approach typically involves the use of oral β-blockers and/or non-dihydropyridine calcium channel blockers, which help reduce heart rate and contractility. The utility of β-blockers has been recently questioned in the randomized MAPLE-HCM trial comparing aficamten and metoprolol, showing no benefit in the metoprolol arm in terms of left ventricular outflow tract (LVOT) gradient reduction and worsening in exercise capacity. [6] Disopyramide, an antiarrhythmic agent with negative inotropic properties, can provide substantial symptomatic benefit, but its efficacy tends to decrease with time, and its anticholinergic side effects limit its use. Although these medications have been the cornerstone of pharmacologic treatment for decades, they do not address the underlying molecular mechanisms of HCM, and evidence supporting their efficacy primarily derives from observational, non-controlled studies. [4,7]

Surgical septal myectomy has long been considered the gold standard treatment for symptomatic patients with oHCM refractory to pharmacological treatment. This procedure is highly effective with low rates of perioperative mortality and morbidity in specialized tertiary centers. Alcohol septal ablation (ASA) relieves left ventricular outflow tract obstruction by inducing targeted myocardial infarction in the hypertrophied septum via ethanol injection, causing wall thinning. However, its applicability is limited by anatomical features, does not address abnormalities in the mitral valve (MV) and its sub-apparatus, and is associated with a higher risk of complete heart block. [8,9]

Recently, the development of myosin inhibitors (CMIs), such as mavacamten and aficamten, has initiated a paradigm shift in the therapeutic approaches for oHCM. These agents selectively inhibit cardiac myosin ATPase activity, thereby reducing hypercontractility and improving myocardial energetic efficiency. By attenuating actin-myosin cross-bridge cycling, CMIs effectively decrease

LVOTO, improve myocardial relaxation and mitigate the pathophysiological burden of HCM. Randomized, placebo-controlled trials such as EXPLORER-HCM and SEQUOIA-HCM have demonstrated the efficacy of CMIs in reducing LVOT gradients, alleviating symptoms, and enhancing functional capacity in oHCM patients. These findings suggest that CMIs may not only provide symptomatic relief, but also potentially impact disease-related structural and functional abnormalities in a significant proportion of patients. [10–12]

The introduction and widespread use of CMIs in clinical practice raise an important question for clinicians: how should the evolving role of pharmacologic treatment influence the decision-making process regarding myectomy? Although these drugs offer a promising treatment for many patients, they may not be a one-size-fits-all solution. [13,14] This point-of-view article explores the evolving role of myectomy in the era of myosin inhibitors, highlighting the strengths and limitations of both therapeutic approaches. We will examine current evidence regarding the efficacy and safety of CMIs, their role in the oHCM treatment algorithm, and their potential influence on decisions regarding surgical intervention. By providing a critical overview of the latest advances, this article aims to guide cardiologists in optimizing treatment choices for patients with this challenging condition.

A brief history of Myectomy

The understanding of the complexity of oHCM has evolved over time, with significant progress in both medical and surgical fields. In 1960, J.F. Goodwin and colleagues [15] presented eight cases of "obstructive cardiomyopathy," one of which was successfully treated by W.P. Cleland two years earlier through partial excision of the septal myocardium via aortotomy. In 1961, Morrow [16] proposed a new method for disrupting the continuity of the sphincter-like contraction ring in the outflow tract. In a subsequent paper, Morrow [17] described 25 patients with "idiopathic hypertrophic subaortic stenosis". Of these patients, five underwent the previously described ventriculomyotomy, which was associated in the subsequent 20 patients with a limited resection of the hypertrophied muscular tissue. The surgical technique involved making two parallel incisions through the endocardium and superficial muscle layers. The first incision was oriented towards the commissure between the left and right coronary leaflets of the valve, while the second incision was located approximately 1 cm to the right and extended 4 cm towards the apex. To access the deeper muscle fibers, digital pressure was applied to split them to a depth of about 1.5 cm. The ridge of tissue between the incisions was then resected.

With the advancement of echocardiography, it became increasingly evident that septal hypertrophy and reduced cavity dimensions were not the only determinants of the obstruction. The focus expanded

to include the mitral valve and the subvalvular apparatus. B. Messmer and colleagues [18] proposed a new surgical approach based on extended and deep septectomy through a transverse aortotomy, combined with the mobilization of the papillary muscles from the left ventricular lateral and posterior walls and partial excision of the hypertrophied portions. D. Cooley, [19] presenting his 20-year experience in treating oHCM from 1970 to 1990, described an alternative approach that combined septectomy with plication of the anterior leaflet parallel to the long axis of the mitral valve to minimize interference with the outflow tract and systolic anterior motion (SAM). Mitral valve replacement was typically reserved for elderly patients, those with moderate to severe valve incompetence, or those who had already undergone ventricular septectomy. Later, vertical plication of the mitral leaflet was abandoned due to concerns that it could alter the coaptation line of the anterior leaflet, potentially resulting in central regurgitation.

Various abnormalities of the mitral apparatus have been reported and studied, including alterations in the number and geometry of papillary muscles, elongation of the leaflets, and retraction or slack of chordae tendineae. These alterations, combined with asymmetrical hypertrophy, are considered the primary mechanism underlying SAM. Consequently, surgical treatment of these abnormalities during extended myectomy is typically performed in most centers. It is worth noting that LVOTO due to SAM can occur in the absence of significant septal hypertrophy. In this context, identifying mitral valve abnormalities is crucial for the evaluation of patients with LVOTO. Multiple alterations of the mitral valve apparatus often coexist. Commonly, a malposition or abnormal number of papillary muscles is found, along with slack or fused chordae tendineae. These associated malformations require the use of different surgical approaches. Other surgical procedures have been proposed and adopted. Shortening the anterior mitral leaflet (AML) using horizontal plication or residual leaflet excision (ReLex) has been developed for mitral leaflet shortening when AML is elongated. Additionally, fibrotic and shortened secondary chordae, which pull the AML into the flow stream, can be effectively treated during myectomy by cutting these chordae. Previous studies aimed at investigating the risk of residual LVOTO after surgical myectomy have highlighted the importance of mitral valve abnormalities and the extent of myectomy. P. Ferrazzi and colleagues [20] proposed the association of myectomy with transaortic resection of thickened secondary chordae, which causes abnormal tethering of the anterior mitral leaflet and anterior displacement of the coaptation point. M. Yacoub and colleagues [21] analyzed the flow alterations in oHCM, which cause a fibrotic reaction of the trigones, reducing the excursions of the subaortic curtain. The subaortic curtain normally moves anteriorly during diastole and posteriorly during systole, allowing relative expansion of the mitral annulus in the first phase and of the LVOT in the latter phase. Therefore, they suggested the removal of excess fibrous tissue

at the trigones to restore the mobility of the subaortic curtain. There is considerable variation in surgical strategies among high-volume referral centers. For instance, the two largest centers in the United States for surgical management of oHCM adopt different approaches to MV intervention. Surgeons at the Cleveland Clinic favor MV repair in up to 25% of myectomy cases and perform MV replacement in approximately 4%, particularly when the interventricular septum measures less than 18 mm. In contrast, the Mayo Clinic rarely performs MV repair (<4%) and reserves MV replacement for patients with intrinsic MV disease. Despite these differences, surgical outcomes are comparable across referral centers. [22]

In cases of severe midventricular obstruction or apical HCM, a combined transaortic and transapical approach may be necessary to alleviate gradients at this level and increase the size of the left ventricular chamber. [23] The persistence of midventricular obstruction has been associated with decreased survival and increased risk of ventricular arrhythmias. Furthermore, apical aneurysms are commonly present and are associated with higher mortality and morbidity, including stroke; thus, aneurysmectomy can be performed safely.

The revolution of Myosin Inhibitors

The discovery of different conformational states of myosin in the early 2000s provided new possibilities for the pharmacological treatment of heart diseases. In 2009, Stewart et al. identified the super relaxed state of cardiac myosin, which is characterized by an ordered helical array and a very slow rate of ATP turnover. [24] The ratio of super-relaxed myosin molecules to the other two states (disordered and active) is essential for long-term sustainability of myocardial work. Genetic variants in sarcomeric genes can cause abnormalities in the structure of the thick myosin filament and myosin hyperphosphorylation, resulting in an increased proportion of myosin molecules accessible to actin. This translates in an increase beta-myosin heads in the disordered-relaxed and active states, and a concomitant reduction of those in the super-relaxed state, intensifying the acto-myosin interaction. [25,26] This leads to a state of hypercontractility in the fibers and to impaired relaxation, associated with a detrimental metabolic balance and oxidative stress due to mitochondrial dysfunction, believed to trigger left ventricular hypertrophy, energy depletion and fibrosis, as well as calcium overload and electrophysiological remodeling of the sarcolemma, facilitating arrhythmogenesis. [26–28]

Mavacamten, the first-in-class myosin inhibitor and the only approved agent to date, was designed to interact with the ATPase catalytic site of the myosin thick filament. [29] The effects of mavacamten

have been investigated in murine models and human iPSC-derived cellular models carrying pathogenic variants in *MYH7* and *MYBPC3*, the main HCM-causing genes. In these models, mavacamten exhibited a dose-dependent reduction in ATPase activity and restored the proper proportion of myosin heads in the super-relaxed state. [26,29,30] Mavacamten has been shown in murine models to reduce profibrotic gene expression and decrease the number of dysregulated mitochondrial genes associated with inefficient energy utilization. [29] Aficamten is the second myosin inhibitor in its pharmacological class to be approved by the FDA. Although it binds to the myosin thick filament at different allosteric modulating sites compared to mavacamten, its ultimate mechanism of action is similar. [31]

The pharmacokinetic profiles of the two molecules differ. Mavacamten is metabolized in the liver by CYP2C19 and has a half-life of 6-9 days in non-poor metabolizers and 23 days in poor metabolizers. Aficamten has a more varied hepatic metabolism and a half-life of 2,8 days. [31,32] The difference in half-life results in a faster onset of action and more rapid wash-out for aficamten, allowing for a two-week titration scheme and a de-escalation of dosage - rather than treatment interruption - in cases where left ventricular ejection fraction (LVEF) falls between 40% and 50%. [12,32] Conversely, mavacamten titration scheme is based on a 4-week evaluation and requires treatment interruption for 4 weeks when the LVEF falls below 50%. [33] Both aficamten and mavacamten have demonstrated marked selectivity for cardiac muscle over fast skeletal muscle and smooth muscle. [26,32]

The role of CMIs as disease-modifying drugs remains to be demonstrated in humans. The phase III clinical trial EXPLORER-HCM showed the efficacy of mavacamten in improving peak oxygen consumption at cardiopulmonary exercise testing (+1.4 mL/kg/min, $p = 0.0006$) with an improvement in effort dyspnea and a reduction in the post-exercise LVOT gradient (-36 mmHg, $p < 0.0001$) in patients with oHCM. Safety and tolerability were similar between groups; serious adverse events occurred in 10 patients (8%) in the mavacamten group and in 11 patients (9%) in the placebo group (11 and 20 events, respectively). [11] In VALOR-HCM, mavacamten vs placebo was evaluated in a population of 112 patients with candidacy for septal reduction treatment (SRT) on top of beta-blockers and/or non-dihydropyridine calcium channel blockers and/or disopyramide therapy, showing a significant reduction in candidacy after 16 weeks in the treatment group (17.9% vs 76.8%, difference 58.9%; 95% CI: 44.0%-73.9%; $P < 0.001$). [34] A recent long-term follow-up update revealed that after 128 weeks of mavacamten therapy, only 1 out of 108 patients met the criteria for surgical intervention, while 7 still opted to undergo myectomy. [35] In the phase III clinical trial SEQUOIA-HCM, treatment with aficamten was associated with an improvement in peak oxygen consumption (+1.7 ml per kilogram per minute; $P<0.001$), in New York Heart Association class and in LVOTO at 24-week fol-

low-up (rest -40 mmHg, p<0.001, post Valsalva -50 mmHg, p<0.001). Serious adverse events occurred in 8 patients (5.6%) in the aficamten group and in 13 patients (9.3%) in the placebo group [12] (Table 1-2).

However, it is worth noting that the mean age of participants in both the EXPLORER-HCM and SEQUOIA-HCM trials was approximately 60 years. Moreover, it remains unclear whether patients with severe LVOTO (i.e., peak gradients exceeding 100 mmHg) would derive comparable benefit from treatment.

A second life for myectomy?

The introduction of CMIs has marked a major turning point in the personalized treatment of oHCM, with the publication of the EXPLORER-HCM trial and the FDA approval of the first CMIs standing as pivotal milestones. [11] These drugs are the first to target the underlying pathophysiologic mechanism of oHCM and have been shown to be highly effective in alleviating symptoms and reducing the LVOT gradient. Their widespread adoption is also raising awareness of the disease among cardiologists and will likely lead to a growing number of patients being identified, thereby expanding the case volume in referral centers. A similar phenomenon has already been observed in other rare cardiac diseases, such as cardiac amyloidosis, where improved recognition and awareness have dramatically increased diagnostic rates and referral patterns in recent years. [36,37]

Yet, LVOTO has a complex and multifactorial patho-physiology, and it is increasingly clear that a one-size-fits-all approach cannot work. From a phenotypic and functional standpoint patients with oHCM present large variability. In that regard, the mechanisms involved in LVOTO may differ significantly amongst patients. Several anatomical factors such as extend and location of hypertrophy, MV leaflet length, MV leaflet relationship, papillary muscle position and mobility, presence of secondary chords, tendinous and muscular connections between MV and subvalvular apparatus with ventricular wall, fibrous subaortic membranes, trigonal scarring, mitral-aortic angulation, are some recognized features known to potentially contribute to LVOTO. [38–40] At a more functional level, hypercontractility, preload conditions and systemic afterload manipulation may further trigger obstructive physiology. For these obvious reasons the therapeutic manipulation of hypercontractile states and septal thickness may only alleviate/relief obstruction in a proportion of patients with oHCM. Understanding a patient's given nature of obstructive pathophysiology may help direct therapeutic options and provide a treatment pathway that do not compromise future options.

Resolution of hypercontractility alone may not be sufficient to abolish obstruction in all patients. Specifically, a pronounced elongation of the MV leaflets, a coaptation of the MV that is very close to the interventricular septum, and a marked deviation of the papillary muscles may render resolution of the hypercontractile state insufficient to effectively eliminate SAM and the resulting LVOTO. [41] Furthermore, particular geometries of the LVOT may increase the likelihood of non-response to CMIs. [42]

Despite the advances of these new drugs, a substantial proportion of patients continue to experience symptoms. According to the latest results of the VALOR-HCM trial, approximately 16% of oHCM patients remained eligible for surgical intervention after 128 weeks of treatment, and around 13.8 % (15 patients) had to suspend therapy because of left ventricular systolic dysfunction, of whom 3 patients had permanent discontinuation of mavacamten (2 for left ventricular ejection fraction < 30% and 1 patient for ventricular ejection fraction < 50% on the lowest dose of 2.5 mg), and in this clinical scenario, rechallenging may be considered unsafe by the physician or undesirable to the patient. [35] Severe LVOTO, refractory symptoms, intolerance to pharmacotherapy, or concomitant use of medications that may significantly interfere with CMIs may still necessitate surgery. Moreover, even patients who respond in terms of symptom relief may retain residual LVOT gradients that drugs cannot eradicate, still warranting consideration for a surgical procedure.

At present, CMIs are not indicated for midventricular obstruction, a setting where surgery not only relieves obstruction but can also remove apical aneurysms, often present in this condition. [43] Alternatively, such phenotype, in patients with deep chests, small aortic annuli or with existent prosthetic aortic valves may also be addressed through a left apical ventriculotomy with excellent outcomes. [44] Correction of obstructive physiology is the norm after these invasive interventions. Importantly, myectomy also offers the advantage of addressing concomitant structural abnormalities, such as mitral or aortic valve pathology, aortic aneurysm, subaortic membrane, coronary artery disease and it can also be combined with Maze-like procedures or left atrial appendage closure to treat atrial fibrillation and reduce the risk of embolic stroke. In addition, certain clinical presentations of concern, such as acute pulmonary oedema or haemodynamic compromise, recurring pre-syncopal or syncopal episodes likely related to LVOTO and not attributed to arrhythmias, may warrant urgent surgical consideration.

Septal myectomy in expert centers may target virtually all patients with oHCM, irrespective of their septal phenotype. In fact, septal myectomy is tailored to each patient anatomy and for this robust multimodality imaging is required to plan the intervention. Even though the best anatomical candidates are patients with isolated basal septal hypertrophy, septectomy may remodel the entire spectrum

of septal anatomies seen in oHCM. Patients with long segment hypertrophy require an expert myectomy surgeon to reach further into the left ventricular cavity to fully eliminate obstruction (and eventually enlarge the left ventricular cavity). It is crucial that septal myectomy is performed at high-volume centers (i.e. > 10 cases per year), as this significantly impacts perioperative mortality and complication rates. [45] In experienced centers, septal myectomy has been shown to significantly reduce LVOTO, improving functional capacity and various patient-reported outcomes (including Kansas City Cardiomyopathy Questionnaire summary score, Patient-Reported Outcomes Measurement Information System, Duke Activity Status Index and European QOL score). [46]

The long-term safety, durability, and practicality of CMIs still require thorough investigation. The cost and accessibility of these new agents, together with the need for frequent echocardiographic evaluations during the up-titration phase, may limit their widespread adoption. Patients' preferences also play a crucial role, as some may prefer to avoid lifelong medication and opt instead for a definitive surgical solution. CMIs are contraindicated during pregnancy, and surgical treatment should be considered in discussions with young symptomatic women with oHCM planning to conceive. Pending large clinical trials on CMIs in the pediatric population, surgical myectomy remains the only therapeutic option for symptomatic oHCM patients refractory to medical therapy within this age group. On the other hand, factors such as high surgical risk, underlying right bundle branch block (due to concerns about developing complete heart block following surgical myectomy), and patients wishing to delay surgery due to life circumstances, may opt for CMIs rather than myectomy; in this scenario, for patients refractory to medical therapy, particularly those who are elderly and frail, ASA may be advisable, provided there is appropriate coronary and septal anatomy, and in the absence of severe LVOTO (i.e., ≥ 100 mmHg) or severe left ventricular hypertrophy (i.e., ≥ 30 mm), following a Heart Team discussion and shared decision-making with the patient. [3] For all these reasons, the choice between pharmacologic and surgical approaches must be tailored to the individual patient, taking into account symptom severity, comorbidities, anatomical suitability for septal reduction therapy, and socioeconomic considerations. [14] The majority of patients enrolled in the EXPLORER-HCM and SEQUOIA-HCM trials were classified as NYHA class II (72% and 76% respectively in the treatment arms), and would not typically be considered candidates for surgical septal reduction. Therefore, the spectrum of patients eligible for CMIs for symptomatic improvement is broader than that for surgical intervention, and the overlap between the two treatment approaches may be minimal in real-world populations (Fig1). In patients with oHCM who remain symptomatic (NYHA class III/IV) despite conventional medical treatment, shared decision-making is essential, considering both the clinical characteristics of the patients and their individual preferences (Fig 2,3).

The loss of surgical skills accrued over fifty years would be a terrible mistake. A similar phenomenon was already observed in Europe in the early 2000s following the introduction of alcohol septal ablation (ASA), when surgical volumes and expertise declined [22,47]. This example demonstrates how quickly surgical expertise can be lost when practice wanes. In the current era, surgery should not merely survive in the shadow of pharmacotherapy: it should evolve.

Beyond the already problematic global lack of surgical expertise [48], the way in which the operation is classically conducted imposes a burden to dissemination of surgical expertise. In classic transaortic open-heart intervention, the septal resection is carried through a narrow space on the arrested heart and without real-time feedback, which limits the teaching-learning opportunities seen in other surgical interventions.

Recently, a new surgical modality of septectomy has emerged, the Wei's operation (transapical beating heart septal myectomy - TA-BSM). [49]This new approach offers a paradigm shift in the way septal myectomy is conducted. For the first time, a truly minimally invasive operation has emerged (without cardiopulmonary bypass), through a limited thoracotomy and in the beating heart under TEE septal resection is tailored. Through real-time feedback after each resection the septectomy is guided and can be supervised, minimizing the changes of iatrogenic septal defects or insufficient resection. It is speculated that transferability of surgical expertise may improve significantly as compared to the standard of care transaortic septal myectomy. [50] The outcomes reported with this new modality of treatment surpass any starting myectomy program experience. [51] For now, however, the device is not available outside China while regulatory work is underway.

At the same time, research is moving forward to identify predictive factors of patient response to CMIs. MV abnormalities and LVOT geometry are key determinants of efficacy, but genetics may also be critical. A sub-analysis of the EXPLORER-HCM trial revealed that genotype-positive patients achieved greater improvement in primary endpoints compared to genotype-negative patients. Specifically, genotype-positive patients had an odds ratio of 4.43 (95% CI, 1.56-12.58), while genotype-negative patients had an odds ratio of 2.52 (95% CI, 0.99-6.42). [52] Complementing these findings, a small retrospective real-world study from a high-volume cardiac surgery center suggested that genotype-positive patients treated with mavacamten were less likely to maintain an indication for septal reduction therapy compared with genotype-negative patients. [53] These results suggest that genotyping could, in the future, help refine patient selection and optimize therapeutic strategies.

Ultimately, given the variability, complexity, and relative rarity of oHCM, referral to specialized HCM centers remains essential, especially for surgical candidates. In these centers, the surgical management of HCM has evolved into a highly individualized procedure, currently associated with a

mortality rate below 1% (around 0.6%) and a complication rate under 5%, including the need for pacemaker implantation (4%), ventricular septal defects (0.3%) with mitral valve replacement as sole operative strategy in 1.8%. [22,54] The best outcomes are achieved through multidisciplinary HCM heart teams, which must include not only expert cardiologists but also skilled surgeons and anesthetists. This integrated model provides the strongest guarantee of both safety and long-term benefit for patients with oHCM [55] (Fig 2,3).

Conclusions

The evolving therapeutic landscape of HCM highlights the need for a personalized, patient-centered treatment approach. Optimal management relies on integrating clinical, imaging, and genetic data to tailor therapy to the specific characteristics of each patient. Multi- and interdisciplinary collaboration between cardiologists, surgeons and anesthetists is crucial for navigating complex decision-making processes and delivering comprehensive care. The advent of CMIs is providing an opportunity to increase the diagnostic yield for this population and eventually offer to a large proportion an effective non-invasive treatment. However, bearing in mind that LVOTO may arise from to a myriad of factors and the appreciation that a proportion of patients under CMIs demonstrate insufficient response, the need for septal reduction treatments remains.

In Europe, surgical expertise in septal myectomy has continued to vanish over the last decades with now very few high-volume centers imposing a risk of survivability of an operation that is considered the gold standard for oHCM and with a track record of more than 6 decades. All efforts must be made to preserve surgical expertise to serve the potentially growing number of patients referred for septal myectomy as disease awareness grows. HCM referral centers should be able to offer the full spectrum of available treatments for oHCM. The surgical option not only is limited to patients unresponsive to medications but may be offered as primary therapeutic intervention in otherwise healthy young patients that are considered low risk surgical candidates. Similarly, the existence of other heart conditions may trigger a surgical option at front (Fig 3). The presence of coronary artery disease, atrial fibrillation, mitral/aortic abnormalities that could be simultaneously addressed at the time of surgery would constitute an indication for surgical intervention. Local and healthcare system factors need to be considered at the time of multidisciplinary discussions as well as well-informed patient's preferences. The availability of a surgical and anesthetic expertise within the HCM referral team is a must to ensure the ability to offer the best possible therapeutic option for oHCM.

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FIGURES LEGEND

Figure 1. The "Iceberg" Model of Left Ventricular Outflow Tract Obstruction in Hypertrophic Cardiomyopathy

Surgical intervention is reserved for a limited subset of patients who fulfill strict surgical criteria (i.e., those exceeding the "surgical threshold"). Conversely, cardiac myosin inhibitors represent a novel disease-modifying therapy with the potential to benefit a wider spectrum of patients, including those who are not candidates for surgery. This model implies that surgical and pharmacologic treatments may overlap in only a minority of patients with obstructive hypertrophic cardiomyopathy

Figure 2. Advantages and disadvantages of myosin inhibitors and surgical myectomy in the treatment of symptomatic patients with obstructive Hypertrophic cardiomyopathy.

Optimal management requires coordinated multidisciplinary collaboration among cardiologists, cardiac surgeons, and geneticists to address complex clinical decision-making and provide comprehensive, individualized patient care. LVEF, Left ventricular ejection fraction; LVOTO, Left ventricular outflow tract obstruction; PM, pacemaker.

Figure 3. Management algorithm for symptomatic obstructive hypertrophic cardiomyopathy.

AF, Atrial fibrillation; CABG, Coronary artery bypass graft; CMIs, cardiac myosin inhibitors; HCM, Hypertrophic cardiomyopathy; LAA, Left atrial appendage; NYHA, New York Heart Association; LV, Left ventricular; LVEF, Left ventricular ejection fraction; LVOT, Left ventricular outflow tract; LVOTO, Left ventricular outflow tract obstruction; non-DHP CCBs, Non-Dihydropyridine Calcium Channel Blockers; oHCM, obstructive hypertrophic cardiomyopathy

List of Abbreviations

ASA = alcohol septal ablation

AML = anterior mitral leaflet

CMIs = cardiac myosin inhibitors

FDA = Food and Drug Administration

HCM = hypertrophic cardiomyopathy

LVOT = left ventricular outflow tract

LVOTO = left ventricular outflow tract obstruction

MV = mitral valve

oHCM = obstructive hypertrophic cardiomyopathy

ReLex = residual leaflet excision

SAM = systolic anterior motion

SRT = septal reduction treatment

TA-BSM = transapical beating heart septal myectomy

TEE = transesophageal echocardiogram

Table 1. Phase III randomized clinical trials on cardiac myosin inhibitors in oHCM.

	Study design	Location of trial	Population	Interventions	Primary endpoints	Results	Secondary endpoints	Results
EXPLORER-HCM [1]	Phase III, RCT, double-blind 30 weeks	USA and Europe (multicenter)	oHCM, LVOT gradient ≥ 50mmHg, LVEF ≥55%, NYHA II/III 251 patients, 123 treated	2.5–15mg mavacamten once daily compared to placebo BB and CCB therapy allowed	pVO2 (CPET) and NYHA class	↑ 19.4% (95% CI 8.7–30.1); p=0.0005	Peak post-exercise LVOT gradient pVO2 (CPET) NYHA class improvement ≥1 KCCQ-CSS HCMSQ-SoB	↓ −35.6 mmHg (95% CI −43.2 to −28.1); p<0.0001 ↑ 1.4 mL/kg/min (95% CI 0.6–2.1); p=0.0006 ↑ 34% (95% CI 22–45); p<0.0001 ↑ 9.1 (95% CI 5.5–12.7); p<0.0001 ↓ −1.8 (95% CI −2.4 to −1.2); p<0.0001
VALOR-HCM [2]	Phase III, RCT, double-blind 16 weeks	USA (multicenter)	oHCM, eligible for SRT in the last 12 months, LVEF ≥60% 112 patients, 56 treated	2.5–15mg mavacamten once daily compared to placebo BB, CCB, and disopyramide therapy allowed	Proceeded with SRT or guideline-eligible to SRT	↓ 58.9% (95% CI 44.0%–73.9%); p<0.001	Peak post-exercise LVOT gradient NYHA class improvement ≥1 KCCQ-23 CSS NT-proBNP hs-cTnI	↓ −37.2 mmHg (95% CI −48.1 to −26.2); p<0.001 ↑ 41.1% (95% CI 24.5–57.7); p<0.001 ↑ 9.4 (95% CI 4.9–14.0); p<0.001 ↓ 0.33 (95% CI 0.26–0.42); p<0.001[a] ↓ 0.53 (95% CI 0.41–

								0.70); p<0.001 [a]
EX-PLORER-CN [3]	Phase III, RCT, double-blind 30 weeks	China (multicenter)	oHCM, LVOT gradient ≥ 50mmHg, LVEF ≥55%, NYHA II/III 81 patients, 54 treated	1–15 mg mavacamten once daily compared to placebo BB or CCB therapy allowed	Valsalva LVOT peak gradient	↓ −70.3 mmHg (95% CI −89.6 to −50.9); p<0.001	Peak resting LVOT gradient Proportion of patients achieving: -Valsalva LVOT peak gradient <30 mmHg -Valsalva LVOT peak gradient <50 mmHg NYHA class improvement ≥1 KCCQ-CSS NT-proBNP hs-cTnI Left ventricular mass index	↓ −55.0 mmHg (95% CI −69.1 to −40.9); p<0.001 ↑ 40.9% (24.4 to 57.5%); p<0.001 ↑ 46.9% (29.6 to 64.2%); p<0.001 ↑ 39.0% (19.9 to 58.1%); p<0.001 ↑ 10.2 (95% CI 4.4 to 16.1); p<0.001 ↓ 0.18 (95% CI 0.13 to 0.24); p<0.001 [b] ↓ 0.34 (95% CI 0.27 to 0.42); p<0.001 [b] ↓ −30.8 g/m² (95% CI −41.6 to −20.1); p<0.001
SEQUOIA-HCM [4]	Phase III, RCT, double-blind	USA and Europe (multicenter)	oHCM, LVOT gradient ≥30 mmHg (rest) and ≥50 mmHg (Valsalva),	Aficamten 5–20 mg once daily compared to placebo BB, CCB, and	pVO□ (CPET)	↑ 1.7 mL/kg/min (95% CI 1.0–2.4), p<0.001	KCCQ at week 24 NYHA class improvement ≥1 at week 24	↑ 7 (95% CI 5–10); p<0.001 ↑ 34.2% (23.4 to 45.0); p<0.001

24 weeks	LVEF ≥60%, NYHA II/III 282 patients, 142 treated	disopyramide therapy allowed	LVOT gradient at Valsalva at week 24	↓ −50 mmHg (−57 to −44); p<0.001
			Proportion of patients achieving Valsalva LVOT gradient <30mmHg at week 30	↑ 45.7% (36.9 to 54.5); p<0.001
			Total duration of SRT eligibility	↓ −78 days (−100 to −56); p<0.001[c]
			KCCQ-CSS at week 12	↑ 7 (5 to 10); p<0.001
			NYHA improvement ≥1 class at week 12	↑ 30.8% (20.6 to 41.0); p<0.001
			LVOT gradient at Valsalva at week 12	↓ −48 mmHg (−55 to −42); p<0.001
			Proportion of patients achieving Valsalva LVOT gradient <30mmHg at week 30	↑ 46.4% (37.3 to 55.5); p<0.001
			Total workload during CPET at week 24	↑ 12.2 Watts (6.4 to 18.0); p<0.001
			Geometric mean proportional	↓ 0.20 (0.17 to 0.23)[d]

							change in NT-proBNP at wk 24	
MAPLE-HCM [5]	Phase III, RCT, double-blind 24 weeks	North America, South America, Europe, Israel, China (multicenter)	oHCM, LVOT gradient ≥30 mmHg (rest) o ≥50 mmHg (Valsalva), LVEF ≥60%, NYHA II/III, KCCQ-CSS ≤90; 175 patients, 88 treated	Aficamten 5–20 mg once daily compared to metoprolol 50-200 mg once daily	pVO□ (CPET)	↑ 2.3 ml/kg/min (95% CI 1.5–3.1), p<0.001	NYHA class improvement ≥1 KCCQ-CSS NT-proBNP LVOT gradient at Valsalva Left atrial volume index Left ventricular mass index	↑ 25 (11 to 39); p<0.001 ↑ 6.9 (2.6 to 11.3); p=0.002 ↓ 0.19 (0.15 to 0.24); p<0.001[e] ↓ −34.9 mmHg (−43.4 to −26.4); p<0.001 ↓ −7.0 ml/m^2 (−9.1 to −4.9); p<0.001 ↓ −4.9 g/m^2 (−11.7 to 2.0); p=0.16

[a] Geometric mean ratios <1.0 represent an ×-fold decrease for mavacamten compared with placebo.

[b] Proportion of geometric mean ratio mavacamten/placebo (95% CI).

[c] SRT eligibility is defined by NYHA functional class III or IV disease and a LVOT gradient (at rest or after the Valsalva maneuver) of at least 50 mm Hg. This analysis was performed only in patients who met these eligibility criteria at baseline.

[d] The proportional change in NT-proBNP was defined as the ratio of the NT-proBNP level (in picograms per milliliter) at week 24 to the baseline NT-proBNP level (in picograms per milliliter).

[e] Proportional change in NT-proBNP level was defined as the ratio of the NT-proBNP level at week 24 to that at baseline.

Abbreviations: BB, β-blockers; CCB, non-dihydropyridine Calcium-Channel Blockers; CI, Confidence interval; CPET, Cardio Pulmonary Exercise Test; HCMSQ-SoB, Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness-of-Breath subscore; hs-cTnI, high-sensitivity cardiac troponin I; KCCQ-CSS, Kansas City Clinical Questionnaire Clinical Summary Score; KCCQ-23 CSS, Kansas City Clinical Questionnaire 23-item Clinical Summary Score; LVEF, left ventricular ejection fraction; LVOT, Left Ventricular Outflow Tract; oHCM, obstructive Hypertrophic Cardiomyopathy; NYHA, New York Heart Association; NT-proBNP, N-terminal pro B-type Natriuretic Peptide; pVO2, peak Oxygen Uptake; RCT, Randomized Clinical Trial; SRT, Septal Reduction Therapy; USA, United States of America.

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Table 2. Long-term extensions studies of the main randomized clinical trials on cardiac myosin inhibitors in oHCM.

	Study design	Location of trial	Population	Interventions	Variable	Results
MAVA-LTE [1]	Single-arm, open-label, ongoing, 252-week LTE of the phase 3 EXPLORER-HCM study [2] Last ad interim analysis 180 weeks	USA and Europe (multicenter)	231 of 244 oHCM patients from EXPLORER-HCM enrolled, all treated Median 166.1 (6.0-228.1) weeks 185 (80.1%) completed the Week 156 visit 99 (42.9%) completed the Week 180 visit	Mavacamten starting dose: 5 mg once daily BB and CCB therapy allowed	Peak resting LVOT gradient, mean (SD) LVOT gradient at Valsalva, mean (SD) Proportion of patients achieving Valsalva LVOT gradient <30mmHg NT-proBNP, median (IQR) EQ-5D-5L score, mean (SD) HCMSQ SoB domain score, mean (SD) NYHA class improvement ≥1 Reduction in LVEF to <50%	↓ −40.3 mmHg (3 ↓ −55.3 mmHg (33.7) 91% ↓ −562 ng/L (−1162.5, −209) ↑ 0.09 points (0.1 ↓ −3.7 points (3.7 77.9% 8.7% [b]
VALOR-HCM LTE [3]	Single-arm, open-label, 128-week LTE of the phase 3 VALOR-HCM study [4]	USA (multicenter)	108 of 112 oHCM patients from VALOR-HCM enrolled, all treated: all 56 patients from original treatment arm (128 weeks treatment period) plus 52 patients from	Mavacamten starting dose: 5 mg once daily BB, CCB, and disopyramide therapy allowed	Proportion of patients proceeding with SRT or remaining guideline-eligible[c]	15.7%[d] ↓ −38.2 mmHg (−42.2 to −30.1) ↓ −59.4 mmHg (−66.0 to −52.7) ↓ −49.6 mmHg (−58.3 to −40.9)

			placebo arm crossed to mavacamten after week 16 (112 weeks treatment period)		Peak resting LVOT gradient, mean (SD)[c] LVOT gradient at Valsalva, mean (SD)[c] Peak post-exercise LVOT gradient [c] NYHA class improvement ≥1[e] NYHA class improvement ≥2[e] KCCQ-23 CSS [c] NT-proBNP, median (95% CI)[c] cTn-I, median (95% CI)[c] Reduction in LVEF to <50%	90.6% 54.2% ↑ 14.2 (10.8 to 17.6) ↓ −481 ng/L (−1168 to −188) ↓ −7.4 ng/L (−16.2 to −1.5) 13,8% [f]
FOREST-HCM [5]	Single-arm, open-label, ongoing, approximately 5 years LTE of the phase 2 REDWOOD-HCM [6] study and of the phase 3 SEQUOIA-HCM study [7] Last ad interim analysis 48 weeks	North America, South America, Europe, Israel, China (multicenter)	213 oHCM patients: 45 from REDWOOD-HCM and 168 from SEQUOIA-HCM 46 patients, with 48 weeks of follow-up, included in the analysis	Aficamten starting dose: 5 mg once daily BB, CCB, and disopyramide therapy allowed	Peak resting LVOT gradient, mean (SD)[g] LVOT gradient at Valsalva, mean (SD)[g] NYHA class improvement ≥1[g] KCCQ-CSSs change, mean (SD)[g]	↓ −40 mmHg (34); p<0.0001 ↓ −53 mmHg (39); p <0.0001 82% ↑ 13 ± 17; p <0.0001 ↓ –3.5 ml/m² (6.6) ↓ –9.0 g/m² (25.2) ↓ –2.6 (5.4); p=0. ↓ –2.2 (6.1); p=0.

	Left atrial volume index, mean (SD)[g]	↓ 63% (95% CI: 5 75%); p<0.0001
	Left ventricular mass index, mean (SD)[g]	↓ 24% (95% CI: 8%- 39%); p=0.0031
	Septal E/e' ratio, mean (SD)[g]	↓ 95%
	Lateral E/e' ratio, mean (SD)[g]	4,3%[i]
	NT-proBNP reduction[g]	
	hs-cTnI reduction[h]	
	Reduction in guideline eligibility for SRT[g]	
	Reduction in LVEF to <50%	

[a] No formal hypothesis testing was performed for efficacy or safety analyses

[b] exposure-adjusted incidence: 2.77/100 patient-years, all recovered LVEF of ≥50%

[c] Total trial population, baseline to week 128, N=108

[d] 7 underwent SRT, 1 was SRT-eligible, and 9 SRT-status unevaluable

[e] baseline to week 128, N=96

[f] 3 patients had permanent discontinuation of mavacamten (2 for LVEF < 30% and 1 patient for LVEF < 50% on the lowest dose of 2.5 mg on 2 different study visit echocardiograms); 12 patients had LVEF improvement to ≥ 50% in follow-up and continued treatment

[g] N=45

[h] N=43

[i] N=46; one of the reduction of LVEF occurred in the setting of alcohol-induced atrial fibrillation; both patients recovered LVEF of ≥50%

Abbreviations: BB, β-blockers; CCB, non-dihydropyridine Calcium-Channel Blockers; EQ-5D-5L, EuroQol – 5 Dimensions – 5 Levels score; HCMSQ-SoB, Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness-of-Breath subscore; hs-cTnI, high-sensitivity cardiac troponin I; IQR, interquartile range; KCCQ-CSS,

Kansas City Clinical Questionnaire Clinical Summary Score; KCCQ-23 CSS, Kansas City Clinical Questionnaire 23-item Clinical Summary Score; LTE, Long-term extension; LVEF, left ventricular ejection fraction; LVOT, Left Ventricular Outflow Tract; oHCM, obstructive Hypertrophic Cardiomyopathy; NYHA, New York Heart Association; NT-proBNP, N-terminal pro B-type Natriuretic Peptide; RCT, Randomized Clinical Trial; SD, Standard deviation; SRT, Septal Reduction Therapy; USA, United States of America.

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Conflicts of Interest

There are no conflicts of interest to disclose

Highlights

1) Cardiac myosin inhibitors, such as mavacamten and aficamten, represent a significant advancement in the personalized treatment of obstructive hypertrophic cardiomyopathy.

2) Surgical septal myectomy remains the gold standard treatment for symptomatic patients with obstructive hypertrophic cardiomyopathy who are refractory to pharmacological therapy, being highly effective with low rates of perioperative mortality and morbidity when performed in specialized, high-volume tertiary centers.

3) The evolving therapeutic landscape of obstructive hypertrophic cardiomyopathy underscores the importance of a personalized, patient-centered treatment strategy, where shared decision-making by the HCM heart team is essential, taking into account both the clinical characteristics of the patient and their individual preferences.

NONINVASIVE RELIEF OF OBSTRUCTION OR MORE APPROPRIATE SURGERY

BROADER RELIEF OF OBSTRUCTION IN NON-SURGICAL CANDIDATES

DISEASE-MODIFYING EFFECTS ON THE MYOCARDIUM

Figure 1

Myosin Inhibitors

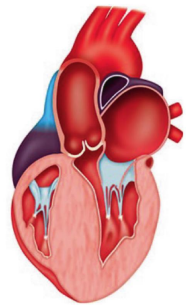
PROS

- ✓ Target the underlying molecular mechanism of disease
- ✓ Non-invasive
- ✓ Improve exercise capacity and symptoms
- ✓ Potential disease-modifying effects (under investigation)
- ✓ Reversible and adjustable therapy

CONS

- ✗ High cost and limited accessibility
- ✗ Lifelong medication
- ✗ Risk of reversible and temporary LVEF reduction
- ✗ Long-term efficacy and safety still under study
- ✗ Only suitable for LVOTO
- ✗ Does not correct structural (e.g. mitral valve) abnormalities

HOCM



Surgical Myectomy

PROS

- ✓ Immediate and definitive
- ✓ Can correct structural abnormalities
- ✓ Proven long-term efficacy
- ✓ No lifelong treatment needed
- ✓ Effective in complex anatomies (midventricular obstruction, apical aneurysm)
- ✓ Improve exercise capacity and symptoms

CONS

- ✗ Invasive procedure, requires hospitalization and recovery
- ✗ Operator and center-dependent outcomes
- ✗ Risk of surgical complications
- ✗ Possible need for PM implantation
- ✗ Less ideal in elderly/high-risk surgical candidates

Figure 2

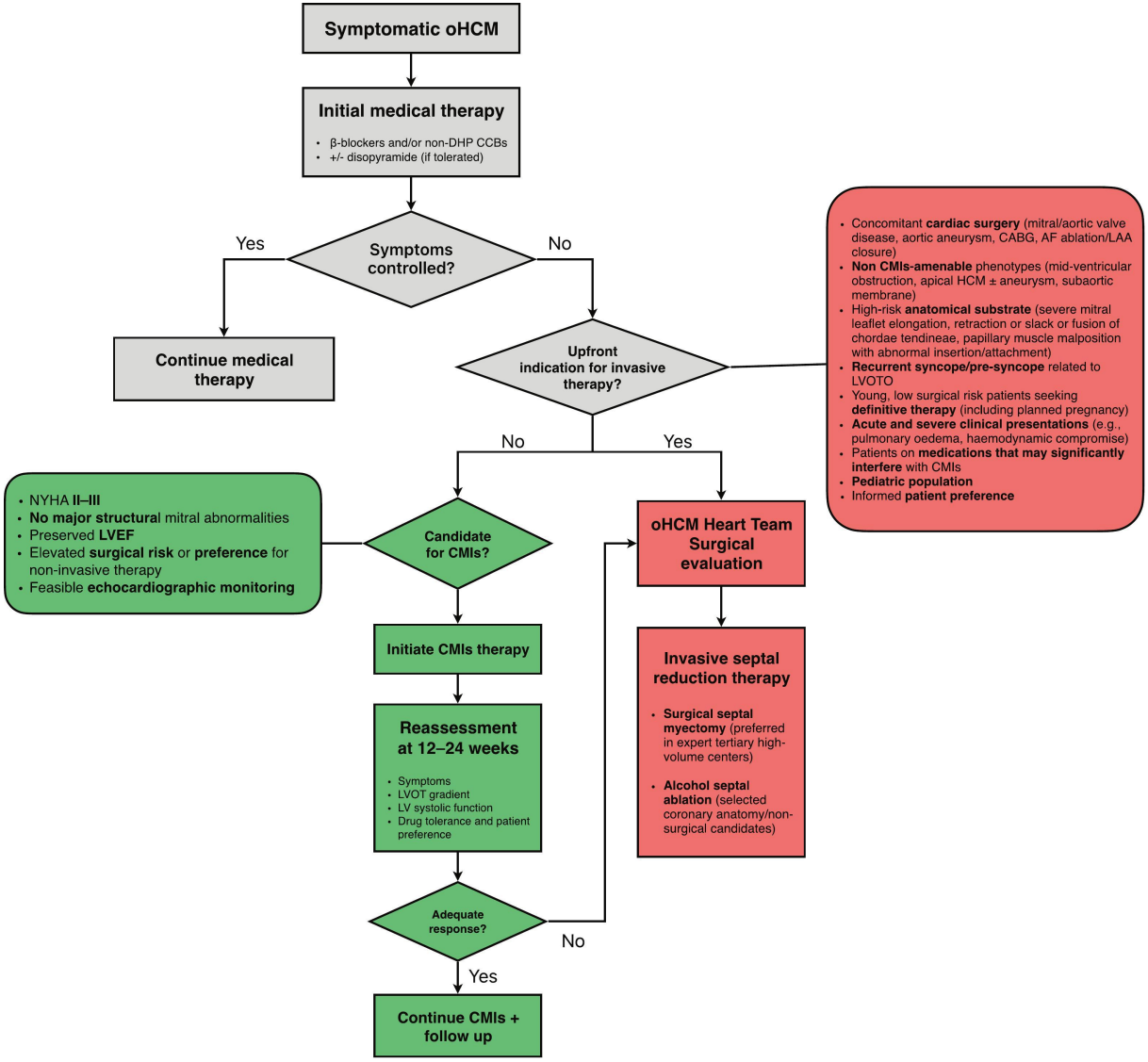

Symptomatic oHCM
Initial medical therapy
β-blockers and/or non-DHP CCBs
+/- disopyramide (if tolerated)
Symptoms controlled?
Yes
No
Continue medical therapy
Upfront indication for invasive therapy?
Concomitant cardiac surgery (mitral/aortic valve disease, aortic aneurysm, CABG, AF ablation/LAA closure)
Non CMIs-amenable phenotypes (mid-ventricular obstruction, apical HCM ± aneurysm, subaortic membrane)
High-risk anatomical substrate (severe mitral leaflet elongation, retraction or slack or fusion of chordae tendineae, papillary muscle malposition with abnormal insertion/attachment)
Recurrent syncope/pre-syncope related to LVOTO
Young, low surgical risk patients seeking definitive therapy (including planned pregnancy)
Acute and severe clinical presentations (e.g., pulmonary oedema, haemodynamic compromise)
Patients on medications that may significantly interfere with CMIs
Pediatric population
Informed patient preference
No
Yes
NYHA II–III
No major structural mitral abnormalities
Preserved LVEF
Elevated surgical risk or preference for non-invasive therapy
Feasible echocardiographic monitoring
Candidate for CMIs?
oHCM Heart Team Surgical evaluation
Initiate CMIs therapy
Invasive septal reduction therapy
Surgical septal myectomy (preferred in expert tertiary high-volume centers)
Alcohol septal ablation (selected coronary anatomy/non-surgical candidates)
Reassessment at 12–24 weeks
Symptoms
LVOT gradient
LV systolic function
Drug tolerance and patient preference
Adequate response?
No
Yes
Continue CMIs + follow up

Figure 3