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Review Article

Current and Future Management of Hypertrophic Cardiomyopathy with Cardiac Myosin Inhibitors

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Abstract

Cardiac myosin inhibitors have changed the landscape for therapy in patients with obstructive hypertrophic cardiomyopathy. Mavacamten, as the first-in-class cardiac myosin inhibitor is FDA approved to improve exercise capacity and symptoms in adults with NYHA class II-III oHCM. This class of drugs offers an alternative to septal reduction therapies and have been found to be well tolerated when monitored. New trials currently in progress studying the cardiac myosin inhibitors hold promising opportunities to change the hypertrophic cardiomyopathy management landscape.

Keywords: Cardiomyopathy, Hypertrophic cardiomyopathy, Obstructive hypertrophic cardiomyopathy, Non-obstructive hypertrophic cardiomyopathy, Cardiac myosin inhibitor

Introduction

Hypertrophic cardiomyopathy is genetic disorder influencing cardiac sarcomeres, and is characterized by left ventricular hypertrophy, hyper contractility, reduced compliance, and left ventricular outflow tract obstruction leading to significant symptomatic burden [1]. Symptomatic disease and genetic carriers have an estimated prevalence 1:200 in general population [2]. Standard of care for medical management was formerly limited to beta blockers (BB), non-dihydropyridine calcium channel blockers (CCB), and disopyramide before consideration of surgical management [3]. However, this does not address the underlying pathophysiology of HCM development. More recently, as understanding of the genetic etiology of the disorder has developed, the medical management has expanded to include disease-modifying interventions. In this review, we discuss the novel cardiac myosin inhibitors and their utilization in practice. We also discuss active trials of this drug class and how positive results would impact current HCM practice.

Dominant mutations in genes that encode the sarcomere of the heart are found in 80% of patients with inherited HCM [4]. These mutated sarcomeres have been demonstrated to have increased ATPase activity, which ultimately is suspected to increase the cardiac contractility in HCM patients [5]. This increased contractility leads to a maladaptive myocardial fibrosis from fibroblast like cells that causes decreased relaxation and progression of heart failure symptoms [6]. A need to address the underlying disease pathophysiology with the increased understanding of the genetic basis of HCM led to the development of mavacamten, the first-in-class cardiac myosin inhibitor. The reduction in ATPase rate leads to less frequent myosin-actin cross bridging, and therefore a decrease in the myocardial contractility [4]. The PIONEER-HCM, EXPLORER HCM, AND VALOR-HCM studies demonstrated mavacamten to be safe and effective in the management of oHCM, leading to an FDA approved medication for use in patients with oHCM [7-9]. This medication is now being used in general practice, and development of next-class-medications have begun.

Aficamten was developed as the next-in-class cardiac myosin inhibitor with three goals in mind: a half-life compatible with once-a-day dosing and steady state plasma concentration within 2 weeks, improved treatability to therapeutic levels, and to design a drug with no CYP450 interactions [10]. The REDWOOD-HCM phase II trial has thus far supported aficamten in these goals, demonstrating improved safety with similar efficacy in oHCM to the mavacamten phase II trial.

The evidence thus far has shown CMI to be an efficacious option for disease modifying treatment previously unavailable to oHCM patients. However, mavacamten and aficamten are both

actively being studied in the management of nHCM, and positive results could change the management landscape of the general patient with HCM.

Literature Review

Upcoming clinical trials on the cardiac myosin inhibitors were found using the ClinicalTrials.gov website. Active trials on hypertrophic cardiomyopathy with interventions of 'mavacamten' or 'aficamten' were selected. Trials were further filtered to include those sponsored by the pharmaceutical company developing the drug, Cytokinetics for aficamten and Bristol-Myers Squibb for mavacamten.

SEQUOIA-HCM is a phase III multicentre, randomized, double-blind, placebo-controlled trial of aficamten, the second-in-class cardiac myosin inhibitor, in oHCM with recent study completion. All included subjects had LVOTG ≥ 30mmHg at rest or ≥ 50mmHg post-Valsalva. The aficamten group demonstrated positive results in the primary endpoint, with an increase in pVO2 (1.74 mL/kg/min [95% CI, 1.04-2.44; $p < 0.0001$]). Full results will likely be released in the coming months [11].

MAPLE-HCM is a phase III multicentre, randomized, double-blind trial with aims to evaluate the efficacy and safety of aficamten to metoprolol in oHCM. All patients will have a LVOTG >30 mmHg at rest and/or ≥ 50 mmHg post-Valsalva. Subjects are divided into either metoprolol or aficamten groups. Primary endpoint is change in pVO2. This trial is the first of its kind utilizing a cardiac myosin inhibitor in place of standard medical therapy of beta blocker. The study is currently in recruitment phase with estimated study completion in 2025 [12].

ODYSSEY-HCM is a phase III, multicentre, randomized, double blind placebo-controlled trial which branched from the MAVERICK_HCM trial, with aims to assess the benefit of mavacamten in nHCM. All patients will have a LVOTG <30 mmHg at rest, and <50 mmHg post-Valsalva. Primary endpoints are change in baseline KCCQ-CSS and change in pVO2 at week 48. The study is currently in recruitment phase with estimated study completion in 2025 [13].

ACACIA-HCM is a phase III, multicentre, randomized, double blinded, placebo-controlled clinical trial of aficamten in patients with nHCM. All patients will have a LVOTG <30 mmHg at rest, and <50 mmHg post-Valsalva. 420 patients are expected to enrol, with half randomized to placebo and half to aficamten. Primary endpoint is symptomatic improvement with KCCQ-CSS questionnaire over 36 weeks, with a planned second part which will extend to 72 weeks. The study is currently in recruitment phase with estimated study completion in 2026 [14].

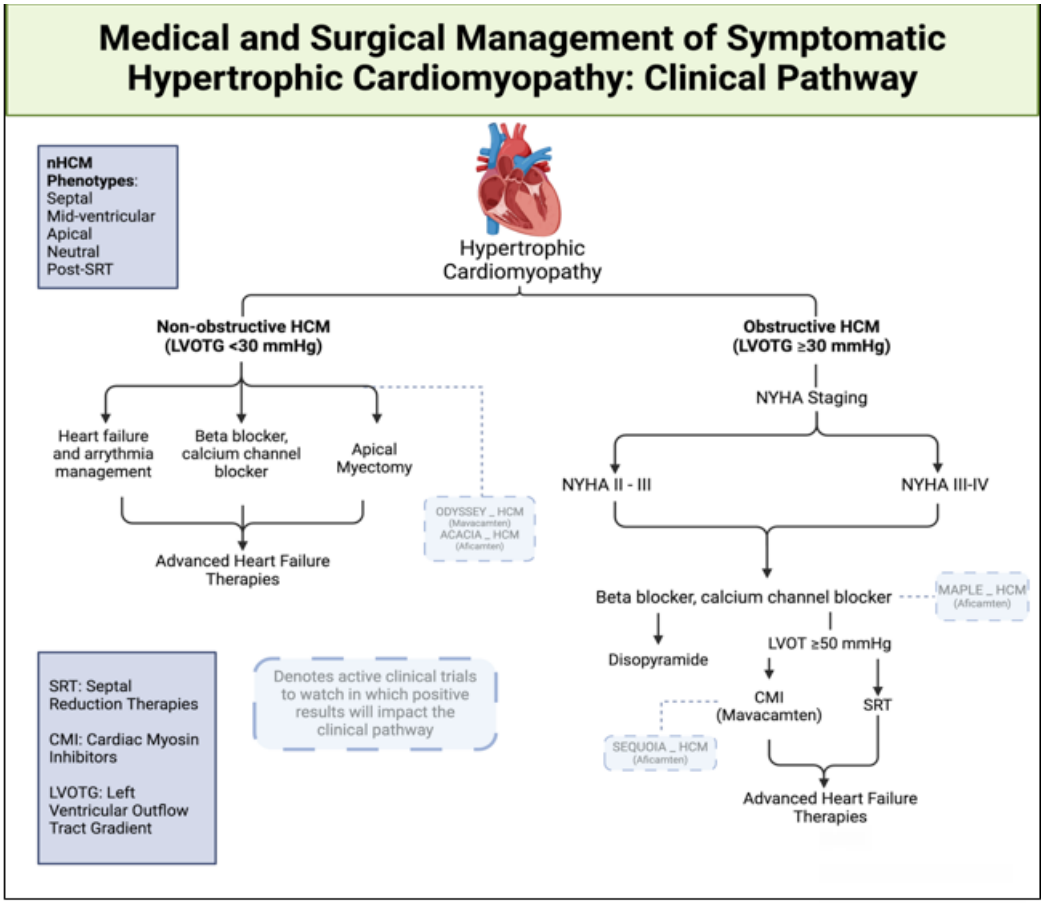
Discussion

The CMI trials of past and future have influenced practice in HCM. According to 2020 AHA/ACC guidelines on HCM, BBs are currently first line in management of oHCM and have demonstrated to be efficacious in reducing resting and exercise gradients, as well as improve symptoms of angina and dyspnoea [15,16]. CCBs are recommended as second line, with evidence supporting improved diastolic filling times and reduced myocardial oxygen demands [17,18]. If persistent symptoms, current guidelines recommend advanced therapy with disopyramide or septal reduction therapies.

The introduction of mavacamten and success of the EXPLORER-HCM and VALOR-HCM trials established the drug as an appropriate option for NYHA II and III oHCM patients with a gradient ≥ 50 mmHg, as well as an alternative to SRT in patients with elevated gradients and NYHA III and IV symptoms. The trials demonstrated symptomatic improvement, as well as a reduction in need for SRT at week 56. Applying mavacamten in these groups will reduce the exposure to risks of SRT, such as ventricular septal defects and complete heart block. The use of CMI is not without adverse effects. As the mechanism of action suggests, excessive negative inotropic effects causing an excessive reduction in ejection fraction to <50% has been noted in both EXPLORER-HCM and VALOR-HCM, however this effect was reversible upon cessation and subsequent dose reduction.

Current Clinical Practice and Future Outlook

Our facility practices by the system seen in (figure 1). Cardiac myosin inhibitors are used as second line therapy in patients with oHCM, post-valsalva gradients ≥ 50 mmHg, and persistent NYHA II-IV symptoms despite the use of standard medical therapy (beta blockers and calcium channel blockers). We prescribe as an adjunct to BB or CCB, and monitor closely for negative inotropic effects with echocardiograms. We avoid use in patients with ejection fraction <55% consistent with the population used in EXPLORER-HCM and discontinue if echocardiogram demonstrates an ejection fraction reduction below 50%. The therapy is offered as an alternative to septal reduction therapies, such as alcohol septal ablation (ASA), septal myectomy (SM) or Septal Scoring Along the Midline Endocardium (SESAME) with influences of symptom burden and shared decision making with the patient goals.



The results of the upcoming aficamten phase III trial SEQUOIA-HCM would provide another option of therapy within cardiac myosin inhibitors, with the elevated safety profile and treatability possibly encouraging its use over the first-in-class CMI. We anticipate the results of MAPLE-HCM to modify the current hierarchy of therapeutic options, with positive results potentially encouraging reaching for a CMI before BB in the appropriate patient population.

Medical management of symptomatic nHCM is a less studied subset of HCM. This group includes patients with septal, mid-ventricular, apical and neutral mutations or post-septal reduction patients with NYHA II-IV symptoms. Standard therapy for this group currently involves beta-blockers and calcium channel blockers, management heart failure and arrhythmias, and apical myectomy for patients who could benefit. However, clinical benefit of these interventions is unclear. ODYSSEY-HCM and ACACIA-HCM are currently active studies utilizing mavacamten and aficamten respectively in this patient population. Positive results will provide evidence-based options for this group and provide first line medical therapy options proven to reduce symptom burden.

Conclusion

HCM is one of the most prevalent etiologies of cardiomyopathy and is associated with symptomatic burden, and development of heart failure, and risk of sudden cardiac death. CMIs provide a therapeutic option targeting the pathophysiology of disease course and have shown success in symptomatic management of oHCM and reduction of LVOTO. Our facility has implemented mavacamten as permitted by FDA approval as adjuncts to current standard of care. Multiple phase III trials are underway that could further adjust the landscape of HCM management. Options for management of nHCM is one of the more exciting aspects of this new drug class, and several phase III trials are actively underway and nearing completion investigating symptomatic improvement in this patient population.

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