For 60 years hypertrophic cardiomyopathy (HCM) has periodically been encumbered by controversy and uncertainty about its management strategies, due largely to heterogeneous clinical presentation and relatively low prevalence in cardiovascular practice. Nevertheless, HCM has now achieved recognition as a contemporary and treatable disease, a stature unanticipated in earlier eras.

Indeed, initially, HCM was a disease for which management was based largely on pharmacotherapy (eg, beta-blockers; verapamil), as well as infrequent high-risk surgical procedures. However, predominantly non-pharmacologic innovations over the last 20 to 25 years have dramatically adjusted patient expectations for longevity and good quality of life, including reversibility of heart failure with surgical myectomy (and its selective alternative alcohol septal ablation).

In the present commentary we discuss the effective treatment modalities currently available for HCM-related heart failure due to left ventricular (LV) outflow obstruction, anticipating the emergence of new medications for symptomatic patients, and the role such therapies may have with respect particularly to time-honored surgical myectomy.

**TREATMENT OF HEART FAILURE**

**Established Invasive Strategies**

**Myectomy Operation**

Surgical septal myectomy (and its percutaneous alternative, alcohol septal ablation) have proved to be the most effective and definitive strategies for reversing progressive symptoms of exertional dyspnea due to LV outflow tract obstruction, in disabled drug-refractory patients (usually New York Heart Association (NYHA) functional class III/IV).

Earlier myectomy is now considered at experienced HCM centers for patients with more mild heart failure symptoms (consistent with NYHA class II) to avoid prolonged LV overload and wall stress.

Myectomy has stood the test of time based on data assembled over >50 years from highly experienced centers worldwide demonstrating the capability of permanently abolishing outflow gradients at rest or with provocation (as well as mitral regurgitation) resulting in normalization of LV pressures, and usually with preservation of systolic function.

Surgical myectomy has become a low risk:high benefit option for patients with LV outflow obstruction and congestive heart failure.
Several drugs have been used to effectively reduce gradient and symptoms in patients with obstructive HCM for about 40 years (Figure). Disopyramide, also a multiple ion channel inhibitor and anti-arrhythmic drug, acts as a more potent negative inotropic agent than beta-blockers and verapamil.

The primary mechanism by which negative inotropic drugs like disopyramide reduce outflow tract gradients is suppression of LV contractility and force of muscular contraction, thereby slowing early systolic flow acceleration from the LV and alleviating hydrodynamic forces on the mitral valve, ie, the pushing force on the protruding leaflets (flow drag).

In an HCM cohort, disopyramide (usually administered with a beta-blocker) reduced LV outflow gradient by >50%, with two thirds of patients symptom and gradient responders in whom timing of surgical myectomy can be potentially delayed for extended periods of time. Notably, disopyramide lowers gradient while preserving LV systolic function with only a small decrease in ejection fraction of 5%.

In observational studies, patients with HCM treated with disopyramide experienced freedom from cardiovascular death including suddenly, and with a total mortality, similar to the general population. Side-effects occurring in a small proportion of patients are vagolytic (usually mitigated by oral pyridostigmine), dry mouth and urinary retention, and prolongation of QT interval is evident in about 6% of patients. Long-term safety of disopyramide is supported by the rarity of proarrhythmia, rendering it safe for outpatient administration. Disopyramide is assigned a class I recommendation by the 2020 American Heart Association/American College of Cardiology guidelines.

Medical Strategies With New Negative Inotropic Agents

In the present treatment era, all pharmaceuticals used in HCM were originally developed for other cardiac conditions. However, there are now 3 new negative inotropic drugs in development which are designed and considered for use in obstructive HCM: mavacamten (MYK-461; MyoKardia/Bristol-Myers-Squibb) which has completed a phase 3 trial and aficamten (Cytokinetics) in a phase 2 trial (Redwood-HCM), both of which are myosin inhibitors, and CT-G20 (Celltrion) a modification of the anti-arrhythmic cibenzoline succinate which has been used in Japan for treatment of symptomatic obstructive HCM.

These drugs may rejuvenate pharmacotherapy for obstructive HCM, notable since they come almost 4 decades after the last medical treatment emerged in this disease, and also following the largely unsuccessful results of 8 clinical drug trials evaluating other therapies: losartan, valsartan, atorvastatin, trimetazidine, ranolazine, antioxidants, spironolactone.

Of the new negative inotropic drugs, the one farthest along in development is the first-generation myosin inhibitor mavacamten (Figure – Panel B). Mavacamten is a small molecule selective allosteric inhibitor of cardiac myosin ATPase tailored to mitigate excessive actin-myosin interaction.

Conventional Medical Strategies

Traditionally, symptomatic obstructive HCM has been treated by a stepwise approach (Figure), initially with maximal pharmacologic therapy aimed at controlling symptoms of functional limitation (predominantly exertional dyspnea). In patients with refractory symptoms (NYHA-class III/IV), or those experiencing unacceptable drug-related side effects, the subsequent recommendation is for surgical myectomy (or selectively, alcohol septal ablation as an operative alternative) (Figure – Panel A). In this respect, drug therapy has always played an important hole in HCM management.
cross-bridge interaction, thereby reducing cardiac contractility. Its primary clinical attribute is reducing LV outflow pressure gradient, based on negative inotropic properties, similar in this regard to disopyramide.

At the time of this writing mavacamten has not achieved approval from the Food and Drug Administration, and what is known about its clinical efficacy actions in HCM is primarily confined to results of a 30-week phase 3 trial (EXPLORER-HCM)\textsuperscript{12}; multicenter, randomized, double-blind, and placebo controlled in 251 patients with LV outflow gradients at rest or with physiologic (exercise) provocation including 123 receiving mavacamten (drug dosage, 2.5–15 mg).

Given the enthusiasm surrounding potential introduction of mavacamten into the HCM therapeutic arena, it is useful to probe the relevant information available from the EXPLORER-HCM trial (Figure – Panel B).

First, compared with placebo, mavacamten demonstrated the capability to reduce outflow gradients in most patients. Nevertheless, only 37% of the patients on mavacamten achieved the combined primary therapeutic end point (compared with 17% on placebo), and nearly two thirds of patients on mavacamten failed to meet this threshold. On the other hand, complete response attributable to mavacamten was achieved in just 27% of patients, defined as gradient <30 mm Hg with restoration to NYHA class I.

While 65% of patients improved by ≥1 NYHA class, symptoms persisted in 50% (class II/III) due largely to the 43% of patients with residual gradients, including...

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**Figure.** Myosin-inhibitors and obstructive HCM.

**A.** Management options and stepwise treatment algorithm for heart failure symptoms. †Not Food and Drug Administration approved at this time. **B.** Notable findings from EXPLORER – HCM phase 3 trial for mavacamten. **C.** Residual gradients (left panel) and failure to achieve symptomatic improvement (right panel) after medical or invasive treatment interventions for obstructive HCM (5, 9, 10, 12, and Harrison DC et al. Circulation 1964; 29: 84–98). *Includes exercise-provoked gradients only; †rest gradient. HCM indicates hypertrophic cardiomyopathy; HF, heart failure; LV, left ventricle; LVOT, left ventricular outflow tract; and NYHA, New York Heart Association. **C.** Reproduced from Maron\textsuperscript{22} with permission from the American Heart Association, Inc. ©2021.
25% with >50 mm Hg the traditional operative cut-off (Figure – Panel B). Historical data show that myectomy and alcohol septal ablation provide a more complete and durable reduction in LV outflow gradient and therefore symptoms than observed with mavacamten.5,11 These data underscore the challenge in treating a mechanical cause of heart failure symptoms pharmacologically, in contrast to invasive septal reduction that directly targets outflow tract anatomy.

In addition, the degree of functional improvement in peak VO2 with mavacamten (1.5 mL/kg/min)2 is similar to the improvement observed with systematic physical exercise in patients with HCM.15 Symptom burden assessed by global health status score with Kansas City Cardiomyopathy Questionnaire15 was improved on mavacamten in about two thirds of patients, while one third experienced no change or worsening of quality of life.

With respect to gradient reduction with mavacamten a cautionary note is appropriate. By virtue of its mechanism reducing contractility (and gradient) with a relatively narrow therapeutic window, an important subset of 7 patients in EXPLORER-HCM (5.6%) also developed systolic dysfunction (ejection fraction) <50% (including 2 patients with LV ballooning syndrome [stress cardiomyopathy] associated with heart failure). Decrease in ejection fraction was substantial in some patients including up to a 57% from baseline (92% to 35%), although reversible with cessation of the drug. The clinical implications of impaired systolic function with mavacamten are unresolved, although in other HCM clinical scenarios ejection fractions <50% have been associated with increased risk for adverse cardiovascular events and heart failure.16

It is notable that the EXPLORER-HCM phase 3 study cohort comprised only a minority of severely symptomatic patients (NYHA functional class III/IV who would be considered candidates for surgical myectomy) while >70% had only mild symptoms at study enrollment (NYHA class II). Therefore, the observed clinical improvement attributed to the drug was largely because of reduction in NYHA class from II to I, and occurring predominantly in older patients (80% were aged >50 years; 34% aged ≥65 years).

Consequently, it is uncertain from EXPLORER-HCM as to whether efficacy of mavacamten in such predominantly less symptomatic and older patients will be translated effectively to younger patients with more advanced symptoms, given that candidates for surgery are predominantly in NYHA class III/IV. Indeed, mavacamten has not been compared directly with established therapies known to reliably relieve gradient and symptoms, such as myectomy and alcohol septal ablation, as well as other drugs such as disopyramide or beta-blockers/verapamil. Data from the phase 3 trial could support administration of mavacamten to patients in whom symptoms may not justify invasive intervention, or in those with advanced heart failure symptoms who are not candidates for surgery or alcohol septal ablation. The ongoing VALOR-HCM study, 16 weeks for the primary end point and with extended follow-up (138 weeks), could possibly provide insights into this issue.17

Some investigators have advanced the idea that myosin inhibitors may convey clinical benefit independent of the gradient lowering effect, ie, as an overall disease modifying therapy for the HCM substrate. In this regard, a recent EXPLORER-HCM substudy reported a substantially 25% reduction in LV mass and up to 8 mm in wall thickness over the short treatment period as well as decrease in left atrial dimension.18 However, it is uncertain whether such LV remodeling associated with mavacamten will increase over time, or represent a favorable morphologic alteration.19 The long-term extension of EXPLORER-HCM may provide additional insights into this issue. Furthermore, mavacamten has not been associated with beneficial clinical effects in symptomatic patients without outflow obstruction.20

Nevertheless, it is likely that myosin inhibitors will require a vigilant monitoring strategy in HCM practice with periodic echocardiographic studies to titrate drug dosage, to monitor an unpredictable interplay of outflow gradient versus ejection fraction (and changes in LV morphology) potentially augmented by the long half-life of mavacamten (ie., 7 days). This is a challenging scenario for “real world” clinical practice environments beyond the boundaries of a highly controlled, clinical dosing trial protocol.

This required surveillance strategy could also escalate what is likely already to be a high cost of a new drug presented to the marketplace, potentially to be taken over many years. Based on some early estimates, there is a cost-efficacy concern similar to that encountered with tafamidis (Vyndaqel) for ATTR-cardiac amyloidosis.21 Furthermore, given the relatively young age (average, about 50 years) when patients elect myectomy,6 treatment with mavacamten will be required for many years if not decades versus the one-time invasive therapy option of surgical myectomy (or alcohol ablation) that also provides the opportunity to be free of drug therapy.

In a recently completed phase 2 clinical trial, the second generation myosin inhibitor aficamten also showed capability for substantial gradient and symptomatic reduction and was well tolerated without discontinuing the drug for systolic dysfunction.15 The relatively short half-life, wide therapeutic window and shallow dose response curve (little ejection fraction variability across a range of drug dose concentrations) of aficamten may have contributed, along with its negative inotropic effect, to the clinical benefit and drug tolerability observed in the REDWOOD-HCM trial.13 More comprehensive assessment of efficacy and safety will emerge from an anticipated phase III clinical trial.
CONCLUSIONS AND PERSPECTIVES

This commentary reviews management strategies for obstructive HCM and heart failure that have been effective over the last 2 decades in reducing HCM morbidity and mortality, including septal reduction with surgical myectomy or alcohol ablation (Figure – Panel C). In addition, we are approaching an era for reinvigorated pharmacotherapy in HCM with novel myosin-inhibitors/ negative inotrope drugs. A measured perspective is justified until more extensive data and experience can be scrutinized over longer periods of time to avoid unrealistic expectations and resolve remaining fundamental questions about the role, efficacy, and safety of these new drugs for obstructive HCM.

While additions to the HCM treatment armamentarium are enthusiastically welcomed (if affordable), there is the concern that initial over-exuberance for myosin-inhibitors could potentially lead to unintended consequences in which there is under-utilization of septal reduction therapies for symptomatic outflow obstruction.

ARTICLE INFORMATION

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Disclosures
Dr M. S. Maron is a consultant for Bristol Myers Squibb, Cytokinetics, Pfizer and Celltrion and has received consulting fees from Celltrion. Dr Rowin has served as a consultant for Bristol Myers Squibb, Cytokinetics, and is a consultant and has a research grant from Takeda Pharmaceuticals. Dr M. S. Maron is a consultant for Cytokinetics and Steering Committee Chair for REDWOOD- HCM phase 2 trial; consultant for Imbria Pharmaceuticals.

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Response to Maron et al

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We read with interest the viewpoint by Maron et al. Several issues raised are addressed in our viewpoint. Nevertheless, we would like to emphasize the following:

1. Cardiac myosin inhibitors (CMIs) directly target the molecular basis of obstructive hypertrophic cardiomyopathy (oHCM) with early evidence for favorable structural remodeling, and ongoing studies investigating their potential for disease modification. Their mechanism of action in targeting the sarcomere does not overlap with any of the other negative inotropes used in oHCM, such as betablockers or disopyramide.

2. We now have evidence of mavacamten efficacy in the VALOR-HCM trial which was conducted in patients with advanced symptoms (93% with NYHA class ≥ III) referred for septal reduction therapy (SRT). In this trial, 17.9% of patients on mavacamten vs 76.8% of patients on placebo still satisfied criteria for SRT after 16 weeks of treatment; an absolute treatment difference of 58.93 (95% CI 43.99, 73.87, p<0.0001).

3. Comparing treatment effect size between a randomized controlled trial - such as Explorer and VALOR - to observational retrospective cohorts – such as all SRT and disopyramide series - is not methodologically justifies.

4. CMIs precisely fill an important gap in the care of oHCM patients. The majority of patients with oHCM have mild to moderate symptoms and would benefit in multiple domains from treatment with CMIs. For patients with severe symptoms, access to the selected experienced centers with excellent SRT outcomes are limited worldwide.

5. While we recommend disopyramide in clinical practice, the drug is not available in many countries and has never been tested in a randomized-controlled trial to assess its treatment effect size.

In conclusion, while we recognize that use of CMIs – if approved – will require caution and continuing surveillance during this early phase, we remain convinced of the ground-breaking potential for myosin modulation in HCM. Hopefully, the wait for real-world evidence is almost over.