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EDITORIAL COMMENT

Aficamten vs Metoprolol: A Turning Point in Obstructive Hypertrophic Cardiomyopathy Care?

The MAPLE-HCM Results

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Historically, beta-blockers have been widely adopted as first-line treatment in symptomatic obstructive hypertrophic cardiomyopathy (oHCM), a practice informed by early evidence from small clinical studies and validated by universal clinical experience.[1-3] Beta-blockers reduce heart rate and may diminish dynamic left ventricular outflow tract (LVOT) obstruction, improve exertional symptoms, and suppress ventricular ectopy. Their physiologic effects on oHCM are indirect, and responses vary considerably among patients. The advantages of beta-blockade often come at the expense of chronotropic incompetence, fatigue, and hypotension.

In contrast, cardiac myosin inhibitors, such as aficamten or mavacamten, represent a conceptual shift in the treatment of oHCM, in that they directly modify the underlying pathophysiology by reducing myosin-actin cross-bridge formation, thereby decreasing hypercontractility and LVOT gradients.[4,5] Such mechanism of action uniquely targets the primary driver of symptoms in patients with obstructive physiology.[4,5]

Although current guidelines still identify beta-blocker therapy as first-line treatment for symptomatic oHCM, accumulating evidence suggests that they may have detrimental effects on exercise capacity, and that their withdrawal in individuals treated with myosin inhibitors is largely neutral from the hemodynamics and symptoms standpoint. Such findings suggest that myosin inhibitors as first-line monotherapy may be advantageous in certain settings.

> *"Rather than just establishing a superiority in controlling symptoms and gradients, great expectations lie in the demonstration that myosin inhibitors may be true modifiers of the long-term trajectory of disease."*

In this issue of *JACC*, the MAPLE-HCM trial provides the first randomized head-to-head comparison of aficamten and a beta-blocker (metoprolol) as first-line therapy in symptomatic oHCM.[6] Its results offer important insights on the potential future role of myosin inhibitors in clinical practice. In MAPLE-HCM, patients receiving aficamten experienced greater improvement in quality of life, limiting symptoms, gradient reduction, and biomarker profile than those receiving metoprolol. These changes appeared early, within weeks, and persisted throughout the 24-week study period.

Based on the results of previous trials with myosin inhibitors, such as Sequoia HCM, these results were reasonably predictable. What was not expected, however, was that metoprolol had limited effect on symptoms and had no measurable effect on any of the other study endpoints, including outflow gradients—in stark contrast from previous (largely

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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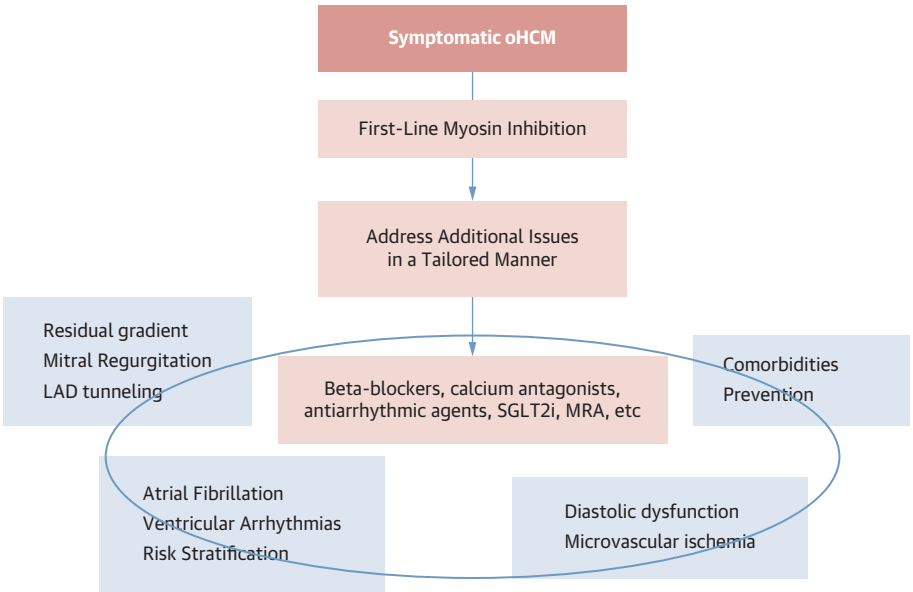
FIGURE 1 Hypothetical Scenario of Future Treatment of Obstructive Hypertrophic Cardiomyopathy (oHCM)



Supporting evidence regarding long-term efficacy and safety will be needed. MRA = mineralocorticoid receptor antagonist; SGLT2I = sodium-glucose cotransporter 2 inhibitor.

nonrandomized) studies, casting a shadow over 5 decades of established practice.

In their subanalysis of MAPLE-HCM, Nassif et al[6] focus on the comparison between aficamten and metoprolol in patient-reported health status benefits, including changes in Kansas City Cardiomyopathy Questionnaire Overall Summary Score (KCCQ-OSS) and Seattle Angina Questionnaire Summary Score (SAQ-SS). Among 175 randomized patients, baseline health status scores were similar between treatment groups. At 24 weeks, aficamten resulted in a greater KCCQ-OSS improvement (adjusted between-group difference +7.8 points; $P < 0.001$ vs metoprolol). When compared with the placebo arm in the Sequoia-HCM trial, aficamten treatment was associated with a 10.1-point improvement, compared with 2.8 points for metoprolol. Notably, large clinical improvements (≥20-point increase) in the KCCQ-OSS were nearly twice as frequent with aficamten than with metoprolol, with a number needed to treat of 4.9, and worsening of symptoms was distinctly less frequent. Overall, these results reflect both the superior hemodynamic and clinical effects of aficamten as well as, in a substantial proportion of patients, the detrimental impact of metoprolol on exercise capacity and quality of life.

The authors are congratulated for a carefully designed and impactful study, expanding the rationale for a potential use of aficamten as first-line therapy in oHCM. Their work reflects scientific rigor, clinical insight, and a clear commitment to improving the care of patients living with HCM. Despite the strengths, however, several limitations warrant consideration.

First, the follow-up duration of 24 weeks is relatively short. Hemodynamic and symptomatic effects of beta-blockers may evolve more gradually, particularly as dose titration often occurs over several months.

Second, although beta-blockers exert modest effects on LVOT obstruction, they also provide some degree of arrhythmic suppression, which may be desirable for symptomatic purposes and relevant in patients at elevated risk of sudden cardiac death.[7] MAPLE-HCM does not address whether aficamten should replace beta-blockers in such patients, or whether combination therapy may be optimal in selected clinical scenarios. A similar issue exists for HCM patients with angina due to microvascular dysfunction.

Third, the trial population size, though sufficient to power the study for the primary endpoint,

remains modest. Larger studies and long-term outcome data will be necessary before guideline recommendations for first-line therapy are revised.

Fourth, not all beta-blockers are equal. Even though metoprolol is one of the most frequently used agents, different molecules may have distinct advantages, and a tailored choice may provide better results than those seen in MAPLE-HCM.

Finally, by design, the trial enrolled patients who were either naive to or tolerated a complete washout of beta-blockers. This may have generated a selection bias whereby those individuals benefiting most from a beta-blocker therapy would have been excluded from enrollment.

While the role of beta-blocker therapy comes under closer scrutiny in oHCM—as has lately occurred in HFpEF and chronic coronary artery disease—several priorities for future research emerge for myosin inhibitors. Rather than just establishing a superiority in controlling symptoms and gradients, great expectations lie in the demonstration that myosin inhibitors may be true modifiers of the long-term trajectory of disease. This concept would once and for all end any debate regarding the best option of first-line therapy for symptomatic patients. Additional extensive further work in multiple directions is needed, as follows.

1) *Long-term outcomes:* Determining durability of symptom benefit, exercise capacity, arrhythmia burden, and heart failure progression will be essential. Most importantly, with the help of large real-world registries, assessing the prognostic impact of myosin inhibition may become possible—using well assembled historical cohorts as comparators.
2) *Patient selection and phenotype alignment:* Not all patients will respond equally. Better identification of responders, as well as those who may require combination therapy or septal reduction intervention, is needed. In that regard, data from EXPLORER HCM demonstrated a decline in left ventricular ejection fraction in a small proportion of patients receiving mavacamten.[4]
3) *Biomarker-guided response assessment:* New approaches for early detection of therapeutic response may complement imaging and functional testing. These may include proteomic and transcriptomic signatures of sarcomere stress or remodeling, genotype-informed risk stratification, and advanced imaging quantifying diastolic function and fiber disarray.
4) *Emerging physiologic signal-based tools:* These remain exploratory and require careful validation before incorporation into routine care, but may also offer value in detecting early functional response. In this regard, our recent proof-of-concept case study demonstrated that treatment-associated changes in myocardial electromagnetic field patterns under mavacamten therapy may be detected early with the use of magnetocardiography.[8]

Soon, if economically sustainable, a first-line approach to oHCM with myosin inhibitors might become the new standard, with subsequent addition of other treatments only when required by each patient's residual needs (**Figure 1**).

And what about beta-blockers? MAPLE-HCM teaches us the humbling lesson that established practice does not always mean best practice. Rather than radically change our approach, however, we should become more mindful of the iatrogenic burden associated with beta-blockers, carefully revise the doses to prevent chronotropic incompetence and side-effects, and resort to myosin inhibition rather than aimlessly increase background therapy when standard doses fail. As always when a radical shift in practice is on the horizon and exciting new options appear, we should be reminded not to throw the baby out with the bath water.

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