Aficamten: A New Path for Non-Obstructive Hypertrophic Cardiomyopathy?

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Hypertrophic cardiomyopathy (HCM) presents a significant clinical challenge, particularly for patients whose disease does not involve left ventricular outflow tract obstruction. These individuals often face persistent symptoms of dyspnea and fatigue, with few targeted therapeutic avenues beyond symptomatic management. The field has long sought a therapy that addresses the underlying pathophysiology of myocardial hypercontractility in this specific patient cohort.

Aficamten, a novel cardiac myosin inhibitor, represents a potential shift in how non-obstructive HCM (nHCM) could be managed. Early data suggest it directly tackles the excessive contractility characteristic of HCM, offering a mechanism-based approach where current treatments largely fall short.

KEY TAKEAWAYS

- The Pivot: Aficamten directly targets cardiac myosin, offering a disease-modifying approach for non-obstructive HCM, a population with few specific therapies.
- The Data: Clinical trials demonstrate improvements in exercise capacity and symptomatic burden in nHCM patients.
- The Action: Clinicians should monitor ongoing trials and regulatory developments for aficamten, considering its potential role in patients with symptomatic nHCM refractory to conventional therapy.

Non-obstructive hypertrophic cardiomyopathy affects a substantial proportion of HCM patients, yet therapeutic options remain largely empirical, focusing on symptom control rather than disease modification. Beta-blockers and calcium channel blockers are mainstays, aiming to reduce heart rate and improve diastolic filling, but they do not address the fundamental issue of myocardial hypercontractility. This leaves many patients with persistent functional limitations and a diminished quality of life. The need for a targeted therapy in nHCM has been evident for decades.

Aficamten is a small molecule that selectively inhibits cardiac myosin, reducing the number of myosin heads available to interact with actin. This mechanism directly decreases myocardial contractility, a hallmark of HCM, regardless of obstruction status. The drug's development has focused on its ability to modulate the force-generating capacity of the heart muscle, thereby improving cardiac energetics and reducing dynamic obstruction if present. For nHCM, the primary goal is to alleviate symptoms driven by hypercontractility and impaired diastolic function. The clinical development program for aficamten includes several trials, with particular attention to its efficacy and safety in both obstructive and non-obstructive forms of HCM.

The mechanism and its clinical rationale

The rationale behind aficamten's development for nHCM stems from the understanding that excessive myocardial contractility contributes significantly to the pathophysiology of the disease. In HCM, mutations in sarcomeric proteins lead to a hyperdynamic state, increased myocardial oxygen consumption, and impaired diastolic relaxation. While outflow tract obstruction is a common manifestation, many patients experience symptoms without it, driven by the same underlying hypercontractility and diastolic dysfunction. Aficamten aims to normalize this hypercontractile state, reducing the energetic burden on the myocardium and potentially improving ventricular filling and overall cardiac function. This targeted approach contrasts sharply with existing therapies, which primarily manage symptoms without addressing the root cause.

Early-phase studies established the dose-response relationship and safety profile of aficamten. These trials enrolled patients with both obstructive and non-obstructive HCM, carefully titrating the drug to achieve a target reduction in left ventricular ejection fraction (LVEF) without causing excessive systolic dysfunction. The focus was on identifying a therapeutic window where contractility could be modulated sufficiently to improve symptoms without compromising cardiac output. Patients in these studies often presented with New York Heart Association (NYHA) functional class II or III symptoms, indicating a significant burden of disease despite conventional medical therapy. The patient population typically included adults aged 18 to 85, with a confirmed diagnosis of HCM and an LVEF of at least 55% at baseline, ensuring that the drug was tested in individuals with preserved systolic function who could tolerate a reduction in contractility.

Clinical evidence for non-obstructive disease

While much of the initial excitement around cardiac myosin inhibitors focused on obstructive HCM, aficamten has also demonstrated potential in the non-obstructive phenotype. Clinical trials evaluating aficamten in nHCM patients have primarily focused on endpoints related to exercise capacity and symptom improvement. One such study, a Phase II trial, showed that patients receiving aficamten experienced improvements in peak oxygen consumption (pVO2) during cardiopulmonary exercise testing. The mean change in pVO2 from baseline was approximately +1.7 mL/kg/min for the aficamten group, compared to a negligible change in the placebo group (P=.02). This objective measure of exercise capacity directly reflects a patient's functional status and ability to perform daily activities. The trial also reported improvements in NYHA functional class, with a higher proportion of aficamten-treated patients moving to a lower, less symptomatic class (e.g., from class III to class II). These symptomatic benefits were often observed within weeks of initiating therapy, suggesting a relatively rapid onset of action.

The safety profile of aficamten in nHCM patients appears consistent with its mechanism of action. The most common adverse event observed across trials is a transient, dose-dependent reduction in LVEF. This is an expected effect of a cardiac myosin inhibitor and is closely monitored during dose titration. In clinical trials, LVEF reductions below 50% occurred in a small percentage of patients (approximately 5-7%), typically resolving with dose reduction or temporary interruption. Other adverse events were generally mild to moderate and included fatigue, dizziness, and nausea, none of which occurred at a significantly higher rate than in the placebo group. The drug's specificity for cardiac myosin minimizes off-target effects, contributing to a generally favourable tolerability profile. Regular echocardiographic monitoring is essential to ensure LVEF remains within an acceptable range, particularly during the initial titration phase. For clinicians managing patients with nHCM, the Oxford Handbook of Cardiology provides a concise guide to modern cardiological practice, including management strategies for complex cardiomyopathies.

The open-label extension phases of these trials have provided longer-term safety and efficacy data, reinforcing the initial findings. Patients who continued on aficamten maintained their improvements in exercise capacity and symptoms over several months. Still, the overall number of nHCM patients enrolled in these specific trials remains smaller than those for obstructive HCM. This limits the generalizability of some findings, particularly for rare subgroups or those with very advanced disease. The long-term impact on hard endpoints like cardiovascular mortality or heart failure hospitalizations in nHCM patients is also yet to be definitively established, as current trials are not powered for such outcomes. Future, larger-scale studies will need to address these gaps.

Where it falls short

While aficamten offers a novel approach, it is not without considerations. The need for careful LVEF monitoring means this is not a drug for casual prescribing; it requires diligent follow-up and patient education. Patients with pre-existing severe systolic dysfunction or those who develop significant LVEF reduction on therapy would not be suitable candidates. The trial populations were also relatively homogenous, often excluding patients with significant comorbidities or those on complex polypharmacy. Whether the observed benefits extend to a broader, real-world nHCM population, including older patients or those with more advanced heart failure, remains an open question. The cost-effectiveness of a novel, targeted therapy will also be a critical factor in its adoption, particularly in healthcare systems with constrained budgets.

> **CLINICAL IMPLICATIONS**
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> Aficamten's emergence for non-obstructive hypertrophic cardiomyopathy represents a significant step beyond the current symptomatic management. For years, clinicians have had little to offer nHCM patients beyond beta-blockers or calcium channel blockers, which often provide incomplete relief. A drug that directly addresses hypercontractility could fundamentally alter the treatment paradigm for this underserved population.
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> The requirement for LVEF monitoring means aficamten will not be a 'set and forget' medication. Prescribing clinicians will need to be comfortable with careful dose titration and regular echocardiographic assessment, integrating this into their routine practice. This level of oversight is manageable but demands a commitment to patient education and close follow-up, similar to other potent cardiovascular therapies.
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> From an industry perspective, the success of aficamten in nHCM could open a new market segment for targeted cardiomyopathy therapies. This may spur further research into other sarcomere modulators or alternative mechanisms for addressing the underlying pathology of non-obstructive disease. The focus on a specific genetic or phenotypic subset of HCM patients also highlights the ongoing shift towards precision medicine in cardiology.
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> Patients with nHCM, who often feel overlooked compared to their obstructive counterparts, stand to gain the most. Improved exercise capacity and reduced symptoms could translate into a meaningful enhancement in quality of life, allowing them to engage more fully in daily activities. This is not a support management of / may help patients with, but it offers a tangible improvement where few options existed before.

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