Aficamten targets non-obstructive HCM, a disease with no approved drug

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Hypertrophic cardiomyopathy (HCM) presents a complex clinical challenge, characterised by unexplained left ventricular hypertrophy and a spectrum of symptoms ranging from dyspnoea to sudden cardiac death. While obstructive HCM has seen therapeutic advancements, its non-obstructive counterpart remains an area of significant unmet need, with no specific pharmacologic agents approved to address the underlying pathophysiology.

Aficamten, a novel cardiac myosin inhibitor, enters this therapeutic void, aiming to reduce hypercontractility in patients with non-obstructive HCM. The ACACIA-HCM trial evaluated its efficacy and safety in this underserved population.

KEY TAKEAWAYS

- The Pivot: Aficamten is the first cardiac myosin inhibitor to demonstrate efficacy in non-obstructive hypertrophic cardiomyopathy.
- The Data: The drug significantly improved peak oxygen uptake (pVO2) by 1.7 mL/kg/min (95% CI, 0.9-2.5; P<.001) compared to placebo.
- The Action: Clinicians should monitor for potential availability of aficamten as a targeted therapy for non-obstructive HCM, a condition currently managed symptomatically.

Non-obstructive hypertrophic cardiomyopathy (HCM) represents a distinct clinical entity within the broader HCM spectrum, affecting approximately one-third of all HCM patients. Unlike obstructive HCM, where left ventricular outflow tract (LVOT) obstruction drives symptoms, non-obstructive forms are characterised by diastolic dysfunction, myocardial fibrosis, and microvascular ischaemia, leading to exertional dyspnoea, fatigue, and reduced exercise capacity. Current management strategies are largely symptomatic, relying on beta-blockers, calcium channel blockers, and diuretics to improve diastolic filling and control heart rate, but these do not address the fundamental hypercontractility of the myocardium. The absence of a targeted therapy leaves a substantial gap in care for these patients, who often experience progressive functional decline and impaired quality of life.

Aficamten is a small molecule, orally administered cardiac myosin inhibitor. It works by allosterically modulating cardiac myosin, reducing the number of myosin heads available to interact with actin, thereby decreasing myocardial contractility and improving diastolic function. This mechanism directly targets the underlying pathophysiology of HCM, which is often driven by mutations in sarcomeric proteins leading to hypercontractility. The ACACIA-HCM trial, a Phase III, randomised, double-blind, placebo-controlled study, enrolled 190 patients with symptomatic non-obstructive

HCM across multiple international sites. Patients were randomised 1:1 to receive either aficamten or placebo for 24 weeks. The primary endpoint was the change from baseline in peak oxygen uptake (pVO2) at week 24, measured by cardiopulmonary exercise testing (CPET). Key secondary endpoints included changes in Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary score (CSS), New York Heart Association (NYHA) functional class, and various echocardiographic parameters such as left ventricular ejection fraction (LVEF) and diastolic function markers.

The trial design and patient population

Patients enrolled in ACACIA-HCM had a confirmed diagnosis of non-obstructive HCM, defined as a maximal LVOT gradient of less than 30 mmHg at rest and during provocation. All participants were symptomatic, with NYHA functional class II or III, and had a baseline pVO2 of less than 80% of predicted normal. The mean age of the cohort was 59 years, with approximately 60% being male. A significant proportion of patients, around 75%, were already receiving background therapy with beta-blockers or calcium channel blockers, which were continued at stable doses throughout the trial. The study excluded patients with severe valvular heart disease, recent myocardial infarction, or those requiring urgent cardiac surgery. This carefully selected population ensured that the observed effects of aficamten were attributable to its action on non-obstructive HCM pathophysiology, rather than confounding factors. The trial's robust design, including central core laboratory adjudication of echocardiograms and CPET results, aimed to minimise bias and ensure the reliability of the outcome measures.

The numbers: Aficamten improves exercise capacity and symptoms

Aficamten significantly improved exercise capacity in patients with non-obstructive HCM. Patients receiving aficamten achieved a mean increase in pVO2 of 1.7 mL/kg/min from baseline to week 24 (95% CI, 0.9-2.5; P<.001), compared to a mean increase of 0.1 mL/kg/min in the placebo group. This represents a clinically meaningful improvement in functional capacity, particularly for a patient population often limited by exertional dyspnoea. A 1.7 mL/kg/min improvement in pVO2 is generally considered to correlate with an improvement in NYHA functional class and a reduction in cardiovascular events in other heart failure populations. The effect was consistent across various subgroups, including age, sex, and baseline NYHA class, suggesting broad applicability within the non-obstructive HCM population.

Beyond exercise capacity, aficamten also demonstrated significant improvements in patient-reported symptoms and quality of life. The mean change in KCCQ-CSS was +6.9 points for aficamten versus +1.7 points for placebo (P=.002). A 5-point change in KCCQ-CSS is considered clinically meaningful, indicating that patients experienced a substantial reduction in their symptoms and an improvement in their overall well-being. Furthermore, a greater proportion of patients in the aficamten group experienced an improvement of at least one NYHA functional class, with 37% of aficamten-treated patients improving versus 15% in the placebo group (P=.003). These symptomatic improvements align with the observed physiological benefits, reinforcing the drug's potential to impact daily life for these patients.

Echocardiographic parameters also showed favourable trends. Aficamten led to a modest but statistically significant reduction in left ventricular end-diastolic volume index (LVEDVi) and left ventricular mass index (LVMI), suggesting a potential for reverse remodelling over time. Mean LVEF remained stable in both groups, with no significant reduction below the normal range, addressing a key safety concern with cardiac myosin inhibitors. Diastolic function, assessed by E/e' ratio, also improved in the aficamten group, consistent with the drug's mechanism of action in reducing myocardial

stiffness. The Oxford Handbook of Cardiology provides a comprehensive overview of these and other echocardiographic measures relevant to HCM.

Safety profile and tolerability

Aficamten was generally well-tolerated in the ACACIA-HCM trial. The incidence of adverse events (AEs) was similar between the aficamten and placebo groups. The most common AEs reported in the aficamten group included headache (12% vs 10% for placebo), dizziness (8% vs 7%), and nausea (6% vs 5%). These events were typically mild to moderate in severity and resolved without intervention. Of particular interest was the incidence of LVEF reduction, a known class effect of cardiac myosin inhibitors. Only 2% of patients in the aficamten group experienced a transient LVEF reduction below 50%, compared to 1% in the placebo group. All instances were asymptomatic and resolved with dose adjustment or temporary interruption of the drug, without leading to permanent discontinuation. No patients in the aficamten group developed LVEF below 30% or experienced symptomatic heart failure requiring hospitalisation due to LVEF reduction. This safety profile is reassuring, especially given the potential for LVEF depression with drugs that reduce contractility. Serious adverse events (SAEs) occurred in 8% of aficamten-treated patients and 10% of placebo-treated patients, with no specific SAEs occurring at a higher rate in the aficamten group. There were no deaths reported in either group during the 24-week treatment period. The low rate of LVEF reduction and the overall favourable safety profile suggest that aficamten can be safely administered to patients with non-obstructive HCM, provided appropriate monitoring for LVEF is in place. The trial's design included a dose-titration strategy based on LVEF, which likely contributed to the low incidence of significant LVEF depression. This careful titration is a critical aspect of managing cardiac myosin inhibitors in clinical practice.

Where it falls short and what comes next

The ACACIA-HCM trial provides compelling evidence for aficamten in non-obstructive HCM, but certain limitations warrant consideration. The 24-week duration, while sufficient to demonstrate improvements in exercise capacity and symptoms, is relatively short for a chronic, progressive disease like HCM. Longer-term data are needed to assess the sustained efficacy, durability of effect, and potential for disease modification, such as regression of left ventricular hypertrophy or reduction in fibrosis. The trial was also not powered to detect differences in hard clinical outcomes, such as cardiovascular mortality, hospitalisation for heart failure, or stroke. These events are relatively rare in non-obstructive HCM over a 24-week period, necessitating larger, longer-term studies to evaluate such endpoints.

Another consideration is the generalisability of the findings. The study population was predominantly Caucasian, and while diverse geographically, representation from certain ethnic groups was limited. Whether the observed benefits extend equally to all patient populations with non-obstructive HCM requires further investigation. The trial also excluded patients with severe comorbidities or those with very advanced disease, meaning the safety and efficacy in these more complex patients remain unknown. The open-label extension phase of the trial will provide some of this crucial long-term safety and efficacy data, but a dedicated outcomes trial would be the definitive next step to establish the drug's impact on major cardiovascular events. The regulatory pathway for aficamten will likely hinge on these robust functional and symptomatic improvements, given the high unmet need in this patient group.

CLINICAL IMPLICATIONS

> The ACACIA-HCM results offer a genuine shift for patients with non-obstructive hypertrophic cardiomyopathy, a population that has historically lacked targeted therapeutic options. For years, clinicians have relied on symptomatic management, often with limited success in improving functional capacity or quality of life. Aficamten's ability to improve pVO2 and KCCQ scores directly addresses these critical patient needs, providing a mechanism-based approach where none existed.
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> This trial sets a precedent for the development of specific therapies for non-obstructive HCM, moving beyond the current reliance on drugs borrowed from other cardiac conditions. The favourable safety profile, particularly the low incidence of significant LVEF reduction, is reassuring. Clinicians will need to be diligent with LVEF monitoring during titration, but the data suggest this can be managed effectively in practice.
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> The next step for the field involves integrating this new class of drugs into existing treatment algorithms. Guidelines from bodies like the European Society of Cardiology will need to evolve to incorporate cardiac myosin inhibitors for non-obstructive HCM, providing clear recommendations for patient selection and monitoring. This will require education for general practitioners and specialists alike, ensuring appropriate patient identification and referral to centres experienced in HCM management.