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Mavacamten: Hope on the Horizon

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Introduction

Take Home Messages

- Mavacamten was recommended by National Institute for Health and Care Excellence (NICE) in September 2023 as a treatment option for NYHA class II-III symptomatic obstructive hypertrophic cardiomyopathy despite optimal medical therapy.
- Mavacamten is well tolerated and provides sustained improvement of symptoms and LVOT gradient reduction in obstructive HCM.
- Mavacamten is not recommended for patients with a left ventricular ejection fraction (LVEF) <55%, as it may reduce LVEF and result in heart failure due to systolic dysfunction.

Mavacamten is the first-in-class, cardiac-specific myosin inhibitor that targets myosin, a protein central to the pathophysiology of obstructive hypertrophic cardiomyopathy (HCM). By reversibly binding to myosin molecules (myosin ATPase), Mavacamten reduces the hypercontractile state of the cardiac muscle by lowering the probability of myosin being in an active state and thereby mitigating associated adverse metabolic effects[1,2] . The United State Food and Drug Administration (FDA) approved Mavacamten in April 2022, following results from the pivotal EXPLORER-HCM trial.[10]

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is predominantly an inherited disease of the heart muscle characterized by left ventricular hypercontractility and impaired relaxation, which may occur with or without dynamic obstruction of the left ventricular outflow tract (LVOT) [3]. In individuals with LVOT obstruction, which affects approximately two-thirds of the HCM population[4], a range of symptoms can occur, including palpitations, chest pain, reduced exercise

tolerance, and syncope[5-8]. These individuals are also at an increased risk of atrial fibrillation, malignant ventricular arrhythmias, sudden cardiac death, and heart failure[3,5-8].

Treatment for obstructive HCM

Standard treatments for obstructive HCM aim to alleviate symptoms using β-blockers, non-dihydropyridine calcium channel blockers and disopyramide. For patients with drug-refractory symptoms, invasive septal reduction therapies (SRT), such as surgical septal myectomy and alcohol septal ablation, can provide effective relief, although the effectiveness of alcohol septal ablation is uncertain in cases of marked septal hypertrophy exceeding 30 mm [9]. Mavacamtem, in contrast, targets the underlying pathophysiology of hypertrophic cardiomyopathy by reducing actin–myosin cross-bridge formation. It has demonstrated efficacy in improving symptoms and reducing the need for septal reduction therapies (SRT).

The National Institute for Health and Care Excellence (NICE) approved Mavacamten in September 2023 for treating obstructive hypertrophic cardiomyopathy (HCM) in adults as a treatment option in patients with HCM and LVOT obstruction who remain symptomatic (NYHA class II to III) despite optimal medical therapy.

Key Clinical Trials Supporting Mavacamten

EXPLORER-HCM Trial[10]

The EXPLORER-HCM trial was a Phase 3 randomized, double-blind, placebo-controlled study involving 251 patients with symptomatic obstructive HCM (NYHA class II–III, LVEF >55%). Obstruction was defined by a peak left ventricular outflow tract (LVOT) gradient >50 mmHg at rest, after the Valsalva manoeuvre, or during exercise. Patients were randomized to receive either Mavacamten (n = 123) or placebo (n = 128) for 30 weeks.

Key findings included:

- 37% of patients on Mavacamten improved in functional capacity (≥1.5 mL/kg/min improvement in peak oxygen consumption (pVO2)) and improvement in symptoms (at least one NYHA functional class reduction), compared to 17% in the placebo group (p = 0.0005).

- Mavacamten reduced LVOT gradients by an average of 36 mmHg, with 74% of patients achieving an LVOT gradient below 30 mmHg.
- 80% of patients on Mavacamten experienced improvement in NYHA class, with 50% reaching NYHA class I by the end of the study.
- Safety and tolerability in the EXPLORER-HCM trial were generally similar between Mavacamten and placebo. However, transient decreases in LVEF to below 50% were observed in 7 patients receiving Mavacamten and 2 patients receiving placebo, necessitating temporary treatment discontinuation. No patient experienced the reduction in LVEF below 30%.

Sub-studies from EXPLORER-HCM demonstrated favourable myocardial remodelling with reductions in myocardial mass, left ventricular wall thickness, and left atrial volume

MAVA-LTE Study[11]

The ongoing MAVA-LTE study is a 5-year open-label extension of the EXPLORER-HCM cohort (n = 231). Interim results indicate sustained reductions in LVOT gradients and NT-proBNP levels, along with improvements in NYHA class over a median follow-up of 62 weeks.

Reported treatment-emergent adverse events included:

- Fatigue: 10.4%
- Dizziness: 10%
- Hypertension: 10%
- Atrial fibrillation: 9.1% (11 new cases in patients without prior history).
- Cardiac failure: 3.5%.

Mavacamten was well tolerated throughout the study period.

VALOR-HCM Trial[12]

The VALOR-HCM trial enrolled 112 symptomatic obstructive HCM patients who were referred for septal reduction therapy (SRT) due to severe drug-refractory symptoms of NYHA III/IV despite maximally tolerated medical therapy. This Phase 3 randomized, double-blind study equally assigned patients to Mavacamten and placebo arms.

Key outcomes included:

- After 16 weeks, only 18% of patients on Mavacamten remained eligible for SRT compared to 77% in the placebo group ($p < 0.001$).
- Mavacamten significantly reduced LVOT gradients (mean reduction: 82 mmHgcompared to placebo (12 mmHg; $p < 0.001$).

- 63% of patients on Mavacamten improved by at least one NYHA functional class, versus 21% in the placebo group.

MAVERICK-HCM Trial[13]

The MAVERICK-HCM trial investigated Mavacamten in 59 patients with symptomatic (NYHA II/III) but non-obstructive HCM. Although the trial demonstrated significant improvements in cardiac biomarkers (NT-proBNP and high-sensitivity cardiac troponin I), the clinical benefits were less pronounced compared to those in obstructive HCM, warranting further research.

Dosing and Monitoring

The standard starting dose of Mavacamten is 5 mg/day, but dose titration is required. Its primary mechanism—reducing hypercontractility—can cause left ventricular systolic dysfunction. Thus, Mavacamten is recommended only for individuals with LVEF >55% and requires regular monitoring for symptoms of heart failure and interval echocardiographic assessments. If LVEF falls below 50% at any time, temporary or permanent discontinuation of treatment is advised.

Conclusions

Growing evidence demonstrates the high potential of Mavacamten in managing symptomatic obstructive HCM and significantly reduce the need for septal reduction therapy (SRT). However, clinical experience remains limited to a relatively small group of patients, specifically symptomatic adults with obstructive HCM and a left ventricular ejection fraction (LVEF) >55%.

Disclosures

The authors declare no conflicts of interest related to this work.

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Abbreviations

HCM	Hypertrophic Cardiomyopathy
LVOT	Left ventricular outflow tract
LVEF	Left ventricular ejection fraction
NYHA	New York Heart Association
NT-proBNP	N-terminal pro-B-type natriuretic peptide
SRT	Septal reduction therapy