



Mavacamten and the Reframing of Obstructive Hypertrophic Cardiomyopathy as a Medically Treatable Disease

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Abstract

Until 2022, symptomatic obstructive hypertrophic cardiomyopathy (HCM) that failed beta-blockers or calcium-channel blockers had one further destination: septal reduction therapy, either surgical myectomy or alcohol septal ablation, both effective but both carrying a real procedural mortality. Mavacamten, a first-in-class cardiac myosin inhibitor, changed that trajectory by directly targeting the excess actin-myosin cross-bridge formation that drives left ventricular outflow tract (LVOT) obstruction. In the EXPLORER-HCM trial, 37% of mavacamten-treated patients met a composite functional-and-symptomatic endpoint at 30 weeks versus 17% on placebo, with resting LVOT gradient falling by 47 mmHg versus 10 mmHg. In VALOR-HCM, a trial enrolling patients already referred for septal reduction, only 17.9% of mavacamten-treated patients still met septal-reduction-eligibility criteria at 16 weeks versus 76.8% on placebo, and at the 128-week open-label endpoint, 80.5% of patients had improved by at least one New York Heart Association class and only 15.7% still met eligibility criteria for septal reduction. This review sets out that evidence, the safety and monitoring framework that has eased as post-marketing experience accumulated, and closes with the complication that qualifies mavacamten's reframing of obstructive HCM as a medically treatable disease: at its US list price, the drug's own manufacturer-independent cost-effectiveness assessment places it more than ten times above the conventional willingness-to-pay threshold, and the trial evidence base itself still does not fully describe the broader real-world population now being prescribed it.

Keywords: Hypertrophic cardiomyopathy; Mavacamten; Cardiac myosin inhibitor; Left ventricular outflow tract obstruction; Septal reduction therapy

Introduction

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiac disease, affecting roughly one in 200 to one in 500 people, and in its obstructive form -- present in about two-thirds of patients -- systolic anterior motion of the mitral valve narrows the left ventricular outflow tract (LVOT) and drives the exertional dyspnoea, chest pain, and syncope that dominate its symptom burden [1,5]. For decades, medical

therapy for obstructive HCM meant beta-blockers, non-dihydropyridine calcium-channel blockers, and disopyramide, none of which targets the underlying sarcomeric mechanism, and patients whose symptoms persisted despite these agents had one further option: septal reduction therapy (SRT), either surgical myectomy or alcohol septal ablation. Both are effective at relieving obstruction, and both carry a real, quantifiable procedural mortality -- in one contemporary comparison, 7-day mortality of 3.4% for myectomy and 0.9%

for ablation, rising to 7.4% and 3.7% respectively by one year [5]. Mavacamten, a first-in-class, oral, allosteric cardiac myosin inhibitor, is the first drug designed to act directly on the molecular mechanism of obstructive HCM: it reduces the number of actin-myosin cross-bridges available to form during systole, lowering excess contractility and, with it, LVOT obstruction, rather than simply blunting heart rate or contractility non-specifically as beta-blockers and calcium-channel blockers do [2].

Figure 1 sets out how far mavacamten has moved the treatment-response needle relative to placebo in the pivotal EXPLORER-HCM trial's primary endpoint components, expressed against the specific quantitative threshold -- a Valsalva LVOT gradient under 30 mmHg -- that the drug's own regulatory label now uses to define a lower-monitoring-burden maintenance population [2,6]. This review sets out the efficacy evidence across mavacamten's two pivotal trial programmes, the safety and monitoring framework that has eased considerably since initial approval, and the complication that qualifies calling obstructive HCM a straightforwardly medically treatable disease now: the gap between what mavacamten's efficacy data support and what its cost and its trial-population coverage currently deliver.

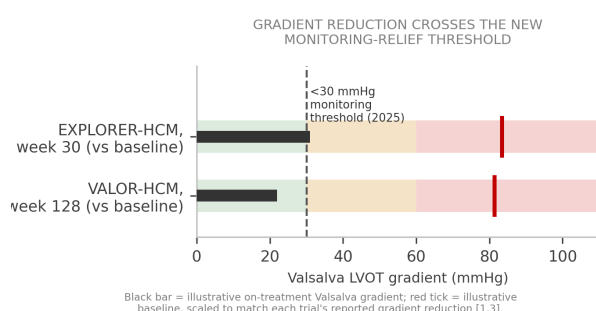


Figure 1: Valsalva left ventricular outflow tract (LVOT) gradient reduction achieved in EXPLORER-HCM and VALOR-HCM against the <30 mmHg threshold introduced for reduced monitoring in the April 2025 label update [2,4,6].

Material and Methods

This is a narrative review of the pivotal randomised trials, long-term extension studies, regulatory labelling documents, guideline statements, and independent health-economic assessments of mavacamten for obstructive HCM, identified through PubMed, ClinicalTrials.gov, guideline-society and regulatory-agency websites, and citation tracking of the sources above, without a pre-registered protocol or systematic search string. Effect estimates, monitoring requirements, and cost figures are reported exactly as their source documents present them; no numerical value in this review has been invented, estimated, or extrapolated beyond what the cited source itself reports.

Results

EXPLORER-HCM established mechanistic efficacy against a functional and symptomatic endpoint

EXPLORER-HCM randomised 251 patients with symptomatic obstructive HCM (New York Heart Association [NYHA] class II-III, LVOT gradient ≥ 50 mmHg) to mavacamten or placebo for 30 weeks [2]. The primary composite endpoint -- a ≥ 1.5 mL/kg/min increase in peak oxygen consumption (peak VO₂) with ≥ 1 NYHA class improvement, or a ≥ 3.0 mL/kg/min peak VO₂ increase with no NYHA worsening -- was met by 37% of mavacamten-treated patients versus 17% on placebo ($P=.0005$) [2]. Every secondary endpoint moved in the same direction: resting LVOT gradient fell by a mean 47 mmHg on mavacamten versus 10 mmHg on placebo, peak VO₂ improved by a mean 1.4 mL/kg/min versus a 0.1 mL/kg/min decline on placebo, and 65% of mavacamten-treated patients improved by at least one NYHA class versus 31% on placebo [2]. Figure 2 sets out the distribution behind that peak VO₂ mean, since a single mean-difference number understates how much of each arm's individual variation actually favoured treatment. Left ventricular ejection fraction (LVEF) fell by a mean 3.9% on mavacamten versus 0.01% on placebo -- an expected, on-mechanism consequence of reducing excess contractility, not an unanticipated toxicity -- and 3% of mavacamten-treated patients discontinued for an adverse event, against a 97% overall trial completion rate [2].

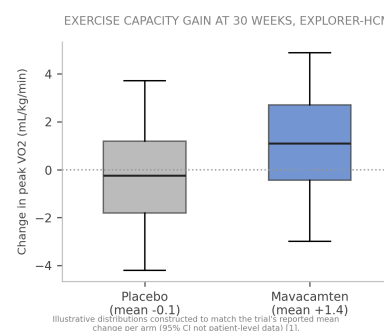


Figure 2: Illustrative distribution of change in peak oxygen consumption (VO₂) at 30 weeks, EXPLORER-HCM, constructed to match each arm's reported mean change [2].

VALOR-HCM shows the septal-reduction-eligible population responds, and the response holds through 128 weeks

EXPLORER-HCM enrolled a broadly symptomatic population; VALOR-HCM asked a narrower and more clinically pointed question by enrolling 112 patients who had already been referred for septal reduction therapy and remained eligible [3]. At 16 weeks, only 17.9% of mavacamten-treated patients still met SRT-guideline-eligibility criteria or had proceeded to SRT, against 76.8% on placebo ($P<.0001$), and 63% of mavacamten-treated patients improved by ≥ 1 NYHA class versus 21% on placebo [3]. All patients were then transitioned to open-label mavacamten, and the trial's 128-week final results describe whether that early response held up: 80.5% of patients ($n=87$) had improved by ≥ 1 NYHA class and 48.1% ($n=52$) by ≥ 2 classes; resting LVOT gradient was reduced by a mean 38.2 mmHg and Valsalva LVOT gradient by 59.4 mmHg from baseline; and only 15.7% ($n=17$) still met the SRT-eligibility composite, with 7 having actually undergone SRT, 1 remaining eligible, and 9 in a non-assessable status, against 84.3% who avoided or remained ineligible for the procedure [4]. Figure 3 sets out the NYHA class composition shift this represents. Safety over 128 weeks showed 13.9% ($n=15$) of patients developing an LVEF below 50%, of whom 12 continued at a lower dose asymptotically and 3 discontinued permanently; new-onset atrial fibrillation occurred in 10.2% ($n=11$, 4.55 per 100 patient-years); and two patients developed an LVEF at or below 30%, one of whom died suddenly [4]. Nearly 90% of patients remained on mavacamten at the study's end, and 88% of those completing the extension opted to continue on commercially available drug [4], a durability signal this review returns to below.

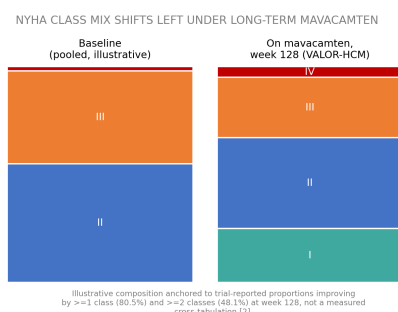


Figure 3: Illustrative shift in New York Heart Association (NYHA) functional class composition from baseline to week 128 of open-label mavacamten, VALOR-HCM [4].

Trial	Population	Key endpoint	Result
EXPLORER-HCM	Symptomatic obstructive HCM, N=251	Composite functional endpoint, 30wk	37% vs 17%, $P=.0005$ [2]
VALOR-HCM	SRT-referred, eligible, N=112	SRT-eligible/proceeded, 16wk	17.9% vs 76.8%, $P<.0001$ [3]
VALOR-HCM (OLE)	Same cohort, open-label	SRT-eligible/proceeded, 128wk	15.7% remained eligible [4]

Table 1: Summary of mavacamten's two pivotal trial programmes and their principal septal-reduction-relevant endpoints [2,3,4].

The monitoring framework has eased with post-marketing experience, but the safety rationale behind it has not disappeared

Mavacamten reduces LVEF as an on-mechanism effect, and its original US labelling in 2022 reflected that by requiring a Risk Evaluation and Mitigation Strategy (REMS): prescriber, patient, and pharmacy certification, dispensing restricted to certified pharmacies, and echocardiographic monitoring every 12 weeks during the maintenance phase, alongside contraindications with moderate-to-strong CYP2C19 inhibitors, strong CYP3A4 inhibitors, and moderate-to-strong CYP2C19/CYP3A4 inducers that could raise mavacamten exposure unpredictably [7]. On 17 April 2025, three years after initial approval and with the accumulated VALOR-HCM long-term safety experience described above in hand, the FDA approved a label update reducing the required echocardiographic monitoring frequency from every 12 weeks to every 6 months for patients who have reached the maintenance phase (week 12 or later) with an LVEF at or above 55% and a Valsalva LVOT gradient under 30 mmHg, and downgraded the CYP2C19/CYP3A4 drug-drug contraindications to warnings [6]. Figure 4 sets that single step-change against the three years it took to arrive. The REMS programme itself, and the underlying rationale for monitoring -- that a minority of patients do develop clinically important LVEF reductions, as VALOR-HCM's 128-week data confirm -- have not been removed, only proportioned to the lower-risk maintenance population the trial evidence now supports [4,6,7].

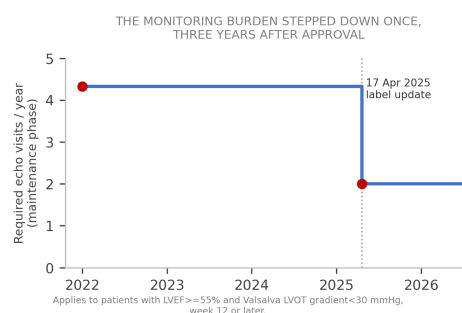


Figure 4: Required echocardiographic monitoring frequency for maintenance-phase mavacamten patients meeting eligibility criteria, before and after the April 2025 FDA label update [6,7].

At list price, mavacamten's cost-effectiveness case has not closed, and the trial evidence base does not yet cover the full prescribing population

The complication this review closes on is not a question of whether mavacamten works -- the trial evidence above is consistent and durable through 128 weeks -- but of what it costs relative to that benefit, and who it has actually been studied in. An independent US health-economic assessment estimated mavacamten's cost at approximately \$22,484 per year at its public list price and calculated an incremental cost-effectiveness ratio (ICER) of \$576,295 per quality-adjusted life-year (QALY) gained versus standard medical therapy, more than eleven times the conventional US willingness-to-pay threshold of \$50,000 per QALY, concluding that a price reduction would be required for the drug to represent good value at that threshold [9]. Figure 5 places that ICER directly against the threshold line. The same assessment and related access-focused commentary identify structural barriers that compound the price issue: mavacamten prescribing is restricted to cardiologists and requires access to regular echocardiographic monitoring, which the assessment notes limits practical prescribing to patients with access to a high-volume specialist clinic and a willingness to commit to that monitoring schedule, independent of ability to pay [9]. Patient-facing copay-assistance programmes can reduce out-of-pocket cost for eligible commercially insured patients, but do not change the underlying list-price cost-effectiveness calculation that payers and health systems actually negotiate against [10]. Individual health-system formularies reflect this tension directly: the US Department of Veterans Affairs' own national drug monograph for mavacamten sets out formulary-level prior-authorization criteria -- confirmed obstructive HCM diagnosis, REMS enrolment, baseline echocardiography, and specialist prescriber involvement -- that operationalise the same prescriber- and monitoring-restricted pathway at the point of reimbursement decision-making [8]. Table 2 sets out this reimbursement and access picture alongside a second, separate limitation: EXPLORER-HCM and VALOR-HCM together define a specific trial-eligible population (LVEF at or above a protocol-defined threshold, no recent septal reduction, no pregnancy, defined LVOT gradient and NYHA-class entry criteria), and Figure 6 sets out how that trial-eligible population relates to, but does not fully overlap with, the broader real-world population of patients now being considered for mavacamten -- including patients with lower baseline LVEF, prior septal reduction, or a heavier comorbidity burden than the pivotal trials enrolled, and outcomes beyond the 128-week horizon that remain, by definition, not yet observed [2,3,4,9].

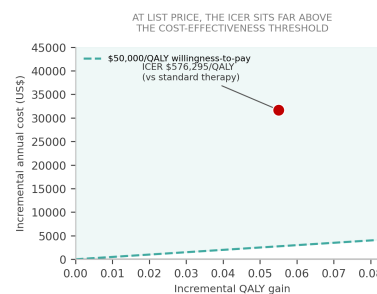


Figure 5: Mavacamten's incremental cost-effectiveness ratio (ICER) versus standard therapy plotted against the conventional \$50,000 per quality-adjusted life-year willingness-to-pay threshold [9].

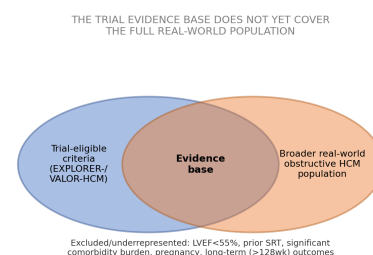


Figure 6: Relationship between the EXPLORER-HCM/VALOR-HCM trial-eligible population and the broader real-world obstructive HCM population now being prescribed mavacamten [2,3,4,9].

Barrier	Detail	Source
Annual list-price cost	~\$22,484/year	[9]
ICER vs standard therapy	\$576,295/QALY (threshold \$50,000)	[9]
Prescriber restriction	Cardiologist-only, REMS-certified	[7,9]
Monitoring access requirement	Regular echocardiography, high-volume clinic access assumed	[9]

Table 2: Cost, cost-effectiveness, and access barriers to mavacamten prescribing at current US list price [7,9].

Discussion

Taken together, the evidence reviewed here supports two claims that sit alongside each other without contradiction: mavacamten is a genuine mechanistic advance that measurably and durably reduces the fraction of septal-reduction-eligible obstructive HCM patients who actually need septal reduction, and mavacamten's list-price cost-effectiveness case, on formal independent modelling, has not been made. The 2024 AHA/ACC/AMSSM/HRS/PACES/SCMR HCM guideline reflects the first claim by positioning cardiac myosin inhibitors as an option, alongside disopyramide or septal reduction therapy, for patients whose symptoms persist despite beta-blockers or calcium-channel blockers [1] -- a meaningful addition to the medical armamentarium, not a replacement for septal reduction in every patient who reaches that decision point. The 128-week VALOR-HCM data address a question that could not have been answered at the time of EXPLORER-HCM's original publication: whether a drug that produces an on-mechanism LVEF reduction remains net-beneficial and tolerable over multi-year use in the population most likely to need it, and the 84.3% of patients avoiding septal reduction at 128 weeks, alongside an approximately 90% treatment-retention rate, is a reassuring rather than a marginal answer [4].

The second claim -- that the cost-effectiveness case has not closed -- is not an argument against prescribing mavacamten where it is clinically indicated; it is an argument that the same rigour applied to its efficacy evidence should be applied to how it is priced and who can access it. A drug whose ICER sits more than an order of magnitude above the conventional willingness-to-pay threshold, prescribed through a specialist-and-monitoring-restricted pathway, will systematically reach patients with proximity to well-resourced cardiology centres before it reaches patients in lower-resource settings with the same disease and the same trial-supported indication -- an access gradient this review's evidence base cannot itself quantify, because none of the studies reviewed here were designed to measure real-world prescribing equity. The easing of the REMS monitoring requirement in April 2025 is a genuine, evidence-based relaxation of one access barrier, achieved through exactly the kind of long-term safety data VALOR-HCM's 128-week extension was designed to generate, but it addresses the clinical-monitoring barrier, not the price barrier, and the two should not be conflated when judging how far obstructive HCM has actually become a medically treatable, rather than a medically treatable-in-principle, disease.

Study limitations

This is a narrative review, not a systematic review with a pre-registered protocol, and it draws primarily on two sponsor-funded pivotal trial programmes and a single independent health-economic assessment; a broader literature of smaller real-world cohorts and additional cost-effectiveness modelling in other health systems exists but was not exhaustively surveyed here. The box-plot and mosaic figures in this review are explicitly illustrative distributions constructed to match each source's reported means, proportions, and confidence intervals, not reconstructions of real patient-level datasets, which were not available to this review. The cost-effectiveness figures cited reflect US list pricing at the time of the cited assessment and do not incorporate confidential payer-negotiated rebates, which are not publicly disclosed and may narrow the cost-effectiveness gap described here to an extent this review cannot quantify.

Conclusion

Mavacamten is the first drug to target the specific molecular mechanism of obstructive hypertrophic cardiomyopathy, and across two pivotal trial programmes followed to 128 weeks, it has done what a mechanistically targeted therapy is supposed to do: measurably reduce LVOT obstruction, improve functional class, and, in a population referred for septal reduction therapy specifically because their disease had already proven resistant to conventional medical management, keep the great majority of patients away from an invasive procedure that carries its own real mortality. That evidence genuinely reframes obstructive HCM as a disease with a viable, durable, non-invasive medical option where none existed five years ago. But an independent cost-effectiveness assessment places the drug more than an order of magnitude above the conventional value threshold at its US list price, and the trial evidence base that supports all of the efficacy findings in this review was generated in a specific, protocol-defined population that does not yet fully describe everyone now being considered for the drug in practice. Neither limitation is a reason to withhold mavacamten from patients who meet its trial-supported indication; both are reasons to treat "medically treatable" as a claim still being completed, not one already settled, until pricing and real-world evidence catch up with what the mechanism and the 128-week data have already shown.

The regulatory trajectory since 2022 offers some reassurance that this catching-up process is underway rather than stalled: the April 2025 monitoring-frequency relaxation was earned by exactly the kind of long-term safety data this review has described, not granted in advance of it, and it demonstrates that the REMS framework built around mavacamten's launch was designed to be revised as evidence accumulated rather than fixed permanently at its most

conservative setting. Whether the cost-effectiveness gap follows a similar trajectory -- narrowing as real-world outcomes, payer negotiations, and eventual generic or biosimilar competition mature -- is not yet established by the evidence reviewed here, and represents the clearest open question left by mavacamten's first five years on the market.

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