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Mavacamten maintenance dose determination: insights into individualised therapy for hypertrophic cardiomyopathy

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ABSTRACT

Aims Mavacamten, the first approved myosin inhibitor for symptomatic obstructive hypertrophic cardiomyopathy (oHCM), addresses hypercontractility and left ventricular outflow tract (LVOT) obstruction. This study evaluates real-world experience with mavacamten, focusing on maintenance dose determination to optimise individual therapy and enhance patient safety.

Methods 36 patients with symptomatic oHCM who completed the initiating phase of mavacamten therapy were analysed. *CYP2C19* genetic testing determined metabolic status prior to treatment. Echocardiographic measurements (eg, LVOT gradient, left atrial volume index, left ventricular ejection fraction (LVEF) and E/E') and biomarkers (high-sensitivity troponin I, N-terminal pro B-type natriuretic peptide (NT-proBNP)) were assessed at baseline and after 3 months. Clinical status was evaluated using New York Heart Association (NYHA) class and Kansas City Cardiomyopathy Questionnaire (KCCQ) score.

Results The mean age of patients was 60.6±12.1, and all had normal *CYP2C19* metabolic status. LVEF was 68% (IQR 8) at baseline and decreased mildly to 60.5% (IQR 7.25; p=0.0004) without cases dropping below 50%. Resting and provoked LVOT gradients decreased from 65 mm Hg (IQR 43.75) and 105 mm Hg (IQR 36.25) to 12 mm Hg (IQR 15.5; p<0.001) and 52.5 mm Hg (IQR 46.5; p<0.001), respectively. NT-proBNP and high-sensitivity troponin I decreased significantly from 1040 ng/mL (IQR 1255) to 285 ng/mL (IQR 483; p=0.0005) and from 11 ng/mL (IQR 15.5) to 10 ng/mL (IQR 5; p<0.0001). Diastolic function improved slightly; and clinically, patients improved significantly, with improvement in NYHA class and increase in KCCQ score. Mean time to reach maintenance dose was 14 weeks, with the necessity of dose adjustments in more than 50% of cases.

Conclusion Mavacamten therapy is safe and effective in the initiating phase. Determination of starting and maximum dose is based on *CYP2C19* metabolic status, while individualised dose adjustments are guided by echocardiographic response to optimise patient safety.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Medical therapy remains the foundation of obstructive hypertrophic cardiomyopathy (oHCM) management; and mavacamten, a novel cardiac myosin inhibitor, has emerged as a promising treatment option for oHCM. Data from randomised controlled trials and ample reports of the real-world use of mavacamten in the USA demonstrated its effectiveness and safety.

WHAT THIS STUDY ADDS

⇒ The novelty of this report is the real-world experience in European patient population and the mandated use of *CYP2C19* testing. Individualised dose adjustments based on echocardiographic response are necessary in about 50% of patients and help optimise patient safety.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ HCM is a highly heterogeneous disease, requiring a personalised approach to optimise outcomes. Long-term data from randomised clinical trials and real-world studies are essential to define the mavacamten's role within the treatment paradigm for oHCM.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is largely a sarcomeric disease characterised by increased left ventricular (LV) wall thickness without an apparent clinical cause of hypertrophy, such as aortic valve stenosis or arterial hypertension, which increase the afterload.[1 2] The distribution and severity of hypertrophy can vary greatly in patients with HCM. About 70% of patients show the obstructive form of the disease with obstruction of the LV outflow tract (LVOT) at rest or on provocation.[1] LVOT obstruction is an independent predictor of death related to HCM and progression of heart failure symptoms.[3] According to current European guidelines, non-vasodilating ß-blockers are the first choice of medical therapy and should be titrated to effectiveness or maximally tolerated doses.

For patients without ß-blocker effectiveness or intolerance, substitution with non-dihydropyridine calcium channel blockers (eg, verapamil, diltiazem) is recommended.[2] If symptoms persist despite these first-line therapies, disopyramide or mavacamten is recommended for symptom management and reduction of LVOT obstruction. Although septal reduction therapies (alcohol septal ablation or septal myectomy) have level I evidence, they are only considered third-line options after pharmacological treatments have been explored.[2]

Mavacamten is a novel first-in-class drug, which specifically targets the underlying pathology of HCM by normalising myosin and actin interactions. This mechanism reduces hyperdynamic contraction, high energy consumption[4] and LVOT gradients while even improving diastolic function.[5 6] Mavacamten is supplied as oral gelatin capsules containing 2.5, 5, 10 or 15 mg with a variable terminal half life (t1/2) that depends mainly on cytochrome P450 2C19 enzyme (CYP2C19) metabolic status. *CYP2C19* poor metabolisers have an increased risk of adverse events due to drug accumulation with increased plasma levels. Therefore, *CYP2C19* genotyping is mandatory in Europe before prescribing mavacamten. In *CYP2C19* poor metabolisers, the starting dose is 2.5 mg/day, with a maximum allowable dose of 5 mg/day. For all other phenotypes of *CYP2C19* metaboliser (intermediate, normal, fast and ultrafast), the starting dose is 5 mg/day, with a maximum dose of 15 mg/day. Regular echocardiographic screening is compulsory to assess LVOT gradients and LV ejection fraction (LVEF) every 4 weeks in the first 3 months and every 12 weeks thereafter. Algorithms for initiation and maintenance dosing, patient monitoring schedules and guidance for treatment interruption or discontinuation are provided in the prescribing information.[7]

Evidence from the phase II and phase III clinical trials[5 6] (EXPLORER-HCM and VALOR-HCM) also demonstrated that mavacamten improves symptoms, exercise capacity and biomarkers of cardiac wall stress and injury, thereby establishing its safety and efficacy. These findings led to the approval of mavacamten by the US Food and Drug Administration (FDA) in April 2022 and by the European Commission in June 2023 for the treatment of adult patients with symptomatic obstructive HCM (oHCM).

Here, we share our initial real-world experience using mavacamten for treatment of patients with symptomatic oHCM, particularly focusing on maintenance dose finding. Understanding the optimal maintenance dose is key to ensuring long-term symptom control and minimising adverse effects.

METHODS

From our ongoing prospective registry, we included 36 patients with symptomatic oHCM with LVOT obstruction (resting or provoked gradient ≥50 mm Hg) who were started on mavacamten therapy between August 2023 and July 2024, according to the European Society of Cardiology guideline recommendations.[2] All patients were on the maximum tolerated doses of ß-blockers or verapamil and underwent *CYP2C19* genetic testing before initiating mavacamten therapy. Echocardiographic evaluations were conducted at baseline and after 4, 8 and 12 weeks of mavacamten therapy and continued further until the maintenance dose was achieved. Dose adjustments were applied during the initiating phase according to the manufacturer's recommendations. Downtitration to 2.5 mg/day was implemented if resting and provoked LVOT gradients fell below 20 mm Hg. Uptitration was considered after 12 weeks for patients with a provoked LVOT gradient above 30 mm Hg and persisting symptoms. However, in contrast to the general recommendations, further uptitration was not pursued if the patient was classified as New York Heart Association (NYHA) class I and had a provoked LVOT gradient below 50 mm Hg, to minimise the risk of LV dysfunction.

Standard four, three and two-chamber views were recorded to evaluate LV function, and LVOT peak gradient was documented at rest and under provocation with the Valsalva manoeuvre. For patients with a resting LVOT gradient >100 mm Hg, provocation manoeuvres were deemed unnecessary, and in cases of LVOT gradient <50 mm Hg, further provocation was done with 15–20 squats. To evaluate changes in LV filling pressures, the left atrial volume index and E/E' were recorded at baseline and after 3 months. Safety outcomes were defined as a drop in LVEF below 50%, cardiac hospitalisation or death. Cardiac hospitalisation was defined as an unplanned hospital admission due to worsening heart failure, arrhythmias (atrial fibrillation, ventricular tachycardia or ventricular fibrillation), cardiac interventions (alcohol septal ablation, septal myectomy, pacemaker implantation) or cardiogenic shock. All patients gave informed consent before taking part in the study.

Statistics

Statistical analysis was performed using GraphPad Prism V.8.1.2. Continuous variables are expressed as mean±SD or median (IQR) (if not normally distributed). The Kolmogorov-Smirnov test was used to test normality of data. Categorical data are described as absolute numbers and percentage (%). Changes in outcome variables between baseline and the 3-month follow-up were assessed using the paired Student's t-test or the non-parametric Mann-Whitney U test, as appropriate.

RESULTS

Between August 2023 and July 2024, thirty-six patients were initiated on therapy with mavacamten. Baseline characteristics are presented in table 1. Patients had a mean age of 60.6±12.1 years (range: 35–87 years), and 17 were female (47.2%). None of the patients had *CYP2C19* poor metabolic status. 11 patients underwent genetic testing; pathogenic or likely pathogenic variants

Table 1 Baseline characteristics of patients initiated on mavacamten

	n=36
Mean age (years)	60.6±12.1
Sex	
Female	17
Male	19
History of septal reduction therapy	5 (13.9%)
Cardiovascular risk factors	
Hypertension	18 (50%)
Diabetes mellitus	4 (11.1%)
Hypercholesterinaemia	15 (41.7%)
Baseline medical therapy	
ß-blockers	25 (69.4%)
Verapamil	6 (16.7%)
None	5 (13.9%)
NYHA class	
III	19 (52.8%)
II	17 (47.2%)
Atrial fibrillation	0
Presence of pacemaker/ICD	9 (25%)
CYP2C19 metabolism: non-poor metaboliser	36 (100%)

CYP2C19, cytochrome P450 2C19 enzyme; ICD, implantable cardioverter defibrillator; NYHA class, New York Heart Association functional class.

in HCM-related genes were identified in six patients. All patients were symptomatic, with 19 patients (52.8%) classified as NYHA class II and 17 patients (47.2%) as NYHA class III. Baseline medication consisted of 25 patients on ß-blockers, six patients on verapamil and five patients who received no medication due to intolerance or hypotension. Baseline medication was continued after initiating mavacamten therapy, and none of the patients were on strong CYP2C19 or CYP3A4 inhibitors that could interfere with mavacamten metabolism. Five patients had a history of septal reduction therapy (alcohol septal ablation >12 months prior) with persistent or recurrent LVOT obstruction, and nine patients had an implanted cardioverter defibrillator.

At baseline, the mean resting LVOT gradient was 67.5±36.7 mm Hg, and the provoked LVOT gradient was 112.2±31.7 mm Hg. After just 4 weeks of treatment with mavacamten, a significant reduction of both resting and provoked gradient was observed, and these reductions persisted throughout subsequent follow-ups during the initiating phase (figure 1A,B). The LV wall thickness measured at the interventricular basal septum at baseline was 21.6±4.4 mm and decreased significantly to 19.6±3.8 mm at follow-up. At baseline, mild mitral regurgitation was present in 29 patients, while five patients had moderate regurgitation. An improvement by one grade was observed in 10 patients (27.8%), while the remaining 26 patients showed no change. The LVEF decreased slightly from 66.9±5.6% at baseline to 64.0±5.1% at 4 weeks and further to 62.8±5.6% at 8 weeks and remained almost stable at 12 weeks with 62.7±5.1% (figure 1C). Though this drop in LVEF was statistically significant, no patient experienced a drop in LVEF below 50%. Hence, no temporary discontinuation of mavacamten was necessary. However, dose adjustments were required in more than 50% of patients. Only in 17 patients the initiating dose of 5 mg matched the maintenance dose. Three patients (8.3%) required a dose reduction to 2.5 mg/day, as recommended by the company, due to a provoked gradient falling below 20 mm Hg (two at 8 weeks, one at 12 weeks). 15 patients had a persistent provoked LVOT gradient >30 mm Hg at 12 weeks, necessitating an increase in mavacamten dose to 10 mg/day; of these,

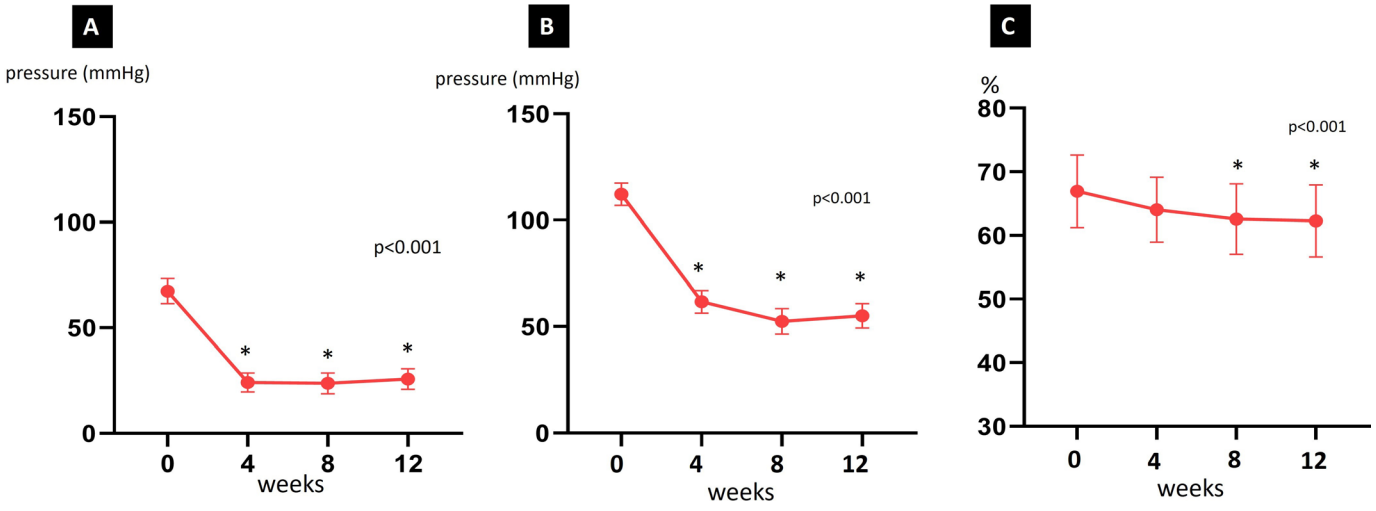

Figure 1 Echocardiographic and functional changes during 12 weeks of mavacamten therapy. (A) Resting LVOT gradients at baseline and after 4, 8 and 12 weeks of mavacamten therapy. (B) Peak LVOT gradients during provocation at baseline and after 4, 8 and 12 weeks of mavacamten therapy. (C) LVEF (in %) at baseline and at 4, 8 and 12 weeks after initiation of mavacamten. LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract.*p<0.001 compared to baseline

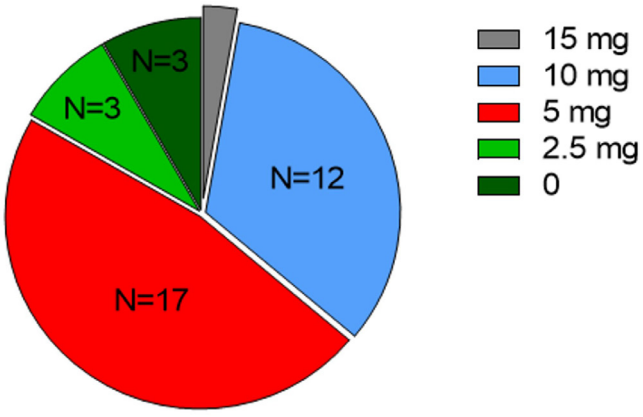

Figure 2 Distribution of mavacamten doses at the end of the initiating phase. oHCM, obstructive hypertrophic cardiomyopathy.

three required a further dose increase to 15 mg/day due to persistently high LVOT gradients. Only one of these three patients achieved significant LVOT gradient reduction and remained on the high (15 mg/day) dose, while the other two patients were discontinued from the medication after 8 weeks on the maximum dose due to lack of response. Both non-responder patients were classified as NYHA class II at baseline and exhibited no clinical improvement, with persistently elevated LVOT gradients exceeding 50 mm Hg even at rest. One additional patient initially had a dose reduction and was ultimately discontinued from mavacamten therapy at the end of the 12-week treatment period due to QT prolongation. This patient subsequently underwent alcohol septal ablation.

The distribution of mavacamten dosage is shown in figure 2. Mean time to reach maintenance dose was 14 weeks (range: 8–20 weeks).

Clinically, significant improvements to mavacamten therapy were observed already after 3 months, with 19 patients (52.8%) classified as NYHA class I, 15 patients (41.7%) as NYHA class II and only two patients (5.5%) remained at NYHA class III (figure 3A). In accordance, the Kansas City Cardiomyopathy Questionnaire (KCCQ) score increased significantly from 52±18 at baseline to 73±20 points at 3 months (p<0.0001), and heart failure marker N-terminal pro B-type natriuretic peptide decreased significantly from 1707±2660 ng/mL to 558±737 ng/mL (p=0.0005) (figure 3B,C).

Regarding safety, no cardiac hospitalisations or deaths occurred during the initiating phase. The medication was generally well tolerated, with only four patients (11.1%) reporting dizziness, which resolved after a few weeks without requiring discontinuation. No syncope or atrial fibrillation occurred in this patient population, and no drop in LVEF <50% was observed. Efficacy and safety parameters are listed in table 2.

DISCUSSION

This study presents an early real-world experience with mavacamten, the first available myosin inhibitor, in patients with oHCM from a specialised HCM centre in Europe. Consistent with findings from randomised controlled trials (RCTs), our data demonstrate that treatment with mavacamten significantly reduces LVOT obstruction and improves clinical symptoms without major adverse events. However, unlike RCTs, which usually include highly selected patient populations and

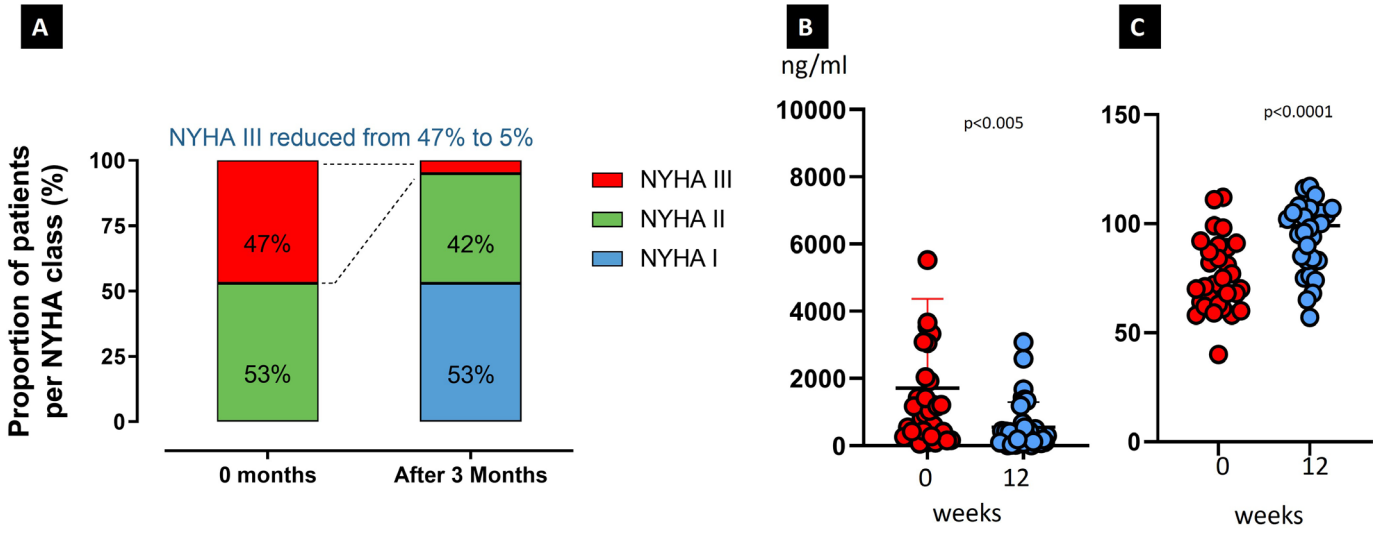

Figure 3 Clinical and biomarker improvements after 12 weeks of mavacamten therapy. (A) Changes in NYHA class distribution from baseline to 12 weeks after initiation of mavacamten therapy. (B) NT-proBNP levels (ng/mL) in patients with obstructive hypertrophic cardiomyopathy (oHCM) at baseline (red) and after (blue) 12 weeks of treatment with mavacamten. (C) KCCQ score in patients with oHCM at baseline (red) and after (blue) 12 weeks of treatment with mavacamten. KCCQ, Kansas City Cardiomyopathy Questionnaire; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA class, New York Heart Association functional class.

Table 2 Efficacy and safety parameters of 36 patients with obstructive hypertrophic cardiomyopathy (oHCM) after 12 weeks of mavacamten therapy

	Baseline	At 12 weeks	P value
LVOT gradient at rest (mm Hg)	65 (IQR 43.8)	12 (IQR 15.5)	<0.0001
LVOT gradient during provocation (mm Hg)	105 (IQR 36.3)	52.5 (IQR 46.5)	<0.0001
Interventricular septum thickness (mm)	21.6±4.4	19.6±3.8	0.003
LVEF (%)	68 (IQR 8)	60.5 (IQR 7.25)	0.0004
NT-proBNP (ng/mL)	1040 (IQR 1255)	285 (IQR 483)	0.0005
High-sensitivity troponin I (ng/mL)	11 (IQR 15.5)	10 (IQR 5)	<0.0001
KCCQ score	52±18	73±20	<0.0001
LAVI (mL/m²)	42.4±14.5	40.1±14.5	0.08
E/E'	15.65 (IQR 6.68)	14.2 (IQR 6.9)	0.03
Safety parameters			
Drop in LVEF <50%	0		
Cardiac hospitalisation	0		
Death	0		
Syncope	0		
AFib	0		

AFib, atrial fibrillation; E/E′, ratio of early mitral inflow velocity to mitral annular early diastolic velocity; KCCQ, Kansas City Cardiomyopathy Questionnaire; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; NT-proBNP, N-terminal pro B-type natriuretic peptide.

adhere to very strict and rigorous protocols, real-world studies are essential for understanding the feasibility and broader applicability of this therapy in routine clinical use.

The clinical status (ie, characteristics and outcomes) observed in our cohort differed widely from those reported in the two main RCTs. In the EXPLORER-HCM trial, 72% of patients were classified as NYHA class II and only 28% as NYHA class III, with 50% of patients reaching NYHA class I after 30 weeks of treatment.[5] Complete response, defined as LVOT gradient <30 mm Hg and NYHA class I, was achieved in 27% of patients. In contrast, in the VALOR-HCM trial, 93% of patients were classified as NYHA class III, of whom 37% showed no clinical response to mavacamten treatment.[6] In our cohort, 53% of patients reached NYHA class I after 12 weeks of treatment, but complete response, as defined in EXPLORER-HCM, was only achieved in 16.7%. Currently, it remains unclear whether further dose increase is truly necessary to reduce the LVOT gradient below 30 mm Hg when patients already achieve clinical benefits, such as reaching NYHA class I. In the present study, the medication dose was not increased further if the patient was classified as NYHA class I and had an LVOT gradient below 50 mm Hg, to minimise the risk of systolic dysfunction. Indeed, none of the patients experienced an LVEF below 50% that necessitated temporary discontinuation of the drug. In contrast, 3.7% of patients in VALOR-HCM and 5.7% of patients in EXPLORER-HCM required discontinuation due to LV dysfunction, possibly reflecting the more rigorous treatment protocols in those trials.

A notable distinction between our study and the RCTs is the inclusion of *CYP2C19* genetic testing, which is not part of the US prescription within the Risk Evaluation and Mitigation Strategy (REMS) programme where the standard starting dose of mavacamten is 5 mg/day. The European Medicines Agency mandates *CYP2C19* genetic testing as an additional safety measure, requiring patients to be tested for specific genetic variants before starting mavacamten treatment.[8] Variants in the *CYP2C19* gene can lead to different metaboliser types: poor, intermediate, extensive, normal or ultrarapid metabolisers. If the test identifies a poor metaboliser status, characterised by two non-functional alleles, such as *2/*2, *2/*3 or *3/*3, the enzyme function is markedly reduced or absent, leading to increased drug levels and a higher risk of adverse effects, such as systolic dysfunction. Poor metabolisers require a starting dose of 2.5 mg/day, with a maximum dose of 5 mg/day, while all other phenotypes can tolerate up to 15 mg/day. In the present study, all 36 patients showed no evidence of being poor metabolisers, and the starting dose was 5 mg/day. However, the prevalence of poor metabolisers varies by ethnicity, being highest in East Asians (11.9%) and Asians (11.1%), followed by African Americans (3.4%), and lowest in Europeans (2.1%).[9] This highlights the importance of personalised approaches in dose optimisation.

In the EXPLORER-HCM trial,[5] dose adjustments were steered by echocardiographic LVOT gradient measurements and mavacamten plasma concentrations. In contrast, the VALOR-HCM trial[6] used core lab measured echocardiographic LV function and LVOT gradients at

rest and during Valsalva provocation, similar to the recommendations in the prescribing information for routine practice. However, the distribution of maintenance doses in the present study differed from that observed in VALOR-HCM. More than 80% of patients reached a maintenance dose of 5 or 10 mg/day after 16 weeks of treatment compared with 57.1% in VALOR-HCM. Only one patient in our group (2.7%) required the maximum dose of 15 mg/day, compared with 21.4% in VALOR-HCM. No patients were discontinued permanently from treatment in VALOR-HCM, whereas in our group we discontinued three patients, one due to QT prolongation and two due to lack of response. The lack of response in these two patients remains unclear but could potentially be attributed to an ultrarapid metabolic status, which induces an increased *CYP2C19* enzyme activity, resulting in reduced plasma drug levels and reduced drug efficacy. In terms of cost-effectiveness, *CYP2C19* genotyping usually does not always cover the full spectrum of alleles. For example, the LightMix kit (Roche Diagnostik Schweiz) used in our centre screens for *2 and *3 loss-of-function alleles to identify poor metabolisers but does not detect the gain-of-function allele *17, which may therefore explain the missed ultrarapid metaboliser status.

Real-world data on mavacamten therapy outside the USA are rare, where its prescription is governed by the REMS programme. At the John Hopkins HCM centre, 66 patients on mavacamten therapy showed results (ie, baseline and outcome data) consistent with our findings; however, 4.5% required temporary discontinuation due to LVEF dropping below 50%.[10] In St Luke's Medical Center (Milwaukee), 31 patients with similar baseline characteristics were treated with mavacamten. Surprisingly, 83.8% had a provoked LVOT gradient <30 mm Hg without requiring any dose adjustments, especially no uptitration.[11] Data from Stanford University on 50 patients enrolled in the FDA-mandated REMS pathway for mavacamten therapy demonstrated significant improvements in wall thickness, mitral regurgitation, LVOT obstruction and clinical symptoms. Only two patients required temporary discontinuation of mavacamten due to an LVEF <50%, and at the most recent follow-up, mavacamten doses were distributed as follows: 2.5 mg in 20%, 5 mg in 38%, 10 mg in 29% and 15 mg in 13% of patients.[12] The largest reported patient population was published from Cleveland Clinic facilities in Ohio and Florida, with 150 patients initiated on mavacamten. Results were similar, with improvements in LVOT gradients and clinical symptoms, with only 2% of patients requiring temporary interruption of mavacamten due to LVEF <50%. Interestingly, 40 patients reported no symptomatic improvement despite significant reductions in Valsalva LVOT gradients.[13] Additionally, only 30% of patients had a Valsalva LVOT gradient >30 mm Hg at 12 weeks, which is much lower compared with our patient group, where 72.2% of patients had LVOT gradient >30 mm Hg, and requiring dose adjustments. A longer treatment duration may reduce this proportion of patients with higher LVOT gradients, as demonstrated in the MAVA-LTE study. At week 84, 85% of patients who were followed up at that time had Valsalva LVOT gradients <30 mm Hg.[14]

These differences in maintenance dose, clinical outcomes and haemodynamic responses underscore the importance of a personalised approach to improve outcomes by tailoring therapy to each patient's tolerability and response. It is becoming evident that HCM is a complex and highly heterogeneous disease, and not all patients will respond to mavacamten. Furthermore, implementing mavacamten therapy is more demanding than first-line medications like ß-blockers or verapamil, requiring multiple echocardiograms for monitoring and dose titration. This places a significant strain on the healthcare system, particularly on outpatient clinics and private practice cardiologists. Aficamten, the second myosin inhibitor that is currently under investigation but yet not available, might address some of the limitations of mavacamten therapy. It has a wider therapeutic window, has a shorter half life of 3–4 days and reaches steady state within 2 weeks. Importantly, aficamten has no substantial cytochrome P450 induction or inhibition in preclinical assessment.[15] The phase II REDWOOD-HCM study and the phase III SEQUOIA-HCM trial demonstrated promising results of aficamten in terms of LVOT gradient reduction and clinical improvement.[16 17]

It is currently unclear whether myosin inhibitors provide a definitive treatment for patients with HCM or merely delay the need for septal reduction therapies. Long-term data from randomised trials and real-world studies are necessary to resolve these unanswered questions. Nevertheless, cardiac myosin inhibitors have the potential to be game changer alternatives in the treatment cascade of HCM.

Limitations

This is a single-centre observational study from a specialised HCM centre, which may limit the generalisability of our findings to the broader oHCM population. Patients treated at a specialised centre have different characteristics or disease severity compared with those managed in a general cardiology setting. The study cohort was limited to 36 patients, and the observation period to a maximum of 20 weeks. Additionally, the lack of a control group makes it difficult to definitively attribute the observed improvements solely to mavacamten, and unmeasured confounding factors might have influenced the outcomes. Furthermore, comprehensive genetic testing was not available for all patients due to insurance restrictions and referring physician decisions, limiting our ability to explore potential genotype-dependent differences in drug response. Similarly, we did not include 24-hour Holter monitoring or cardiac MRI in our protocol, as our primary focus was on real-world dosing experience. However, future studies should consider these modalities to assess arrhythmic burden and myocardial fibrosis

progression under mavacamten therapy. Finally, some outcome measures, such as NYHA class and KCCQ score, are based on subjective assessments and may be subject to bias. Larger, multicentre and multinational registers with long-term follow-up are needed to validate the role of mavacamten in the therapeutic strategies for patients with HCM.

CONCLUSION

Based on these real-world data, we conclude that treatment of patients with oHCM with the only myosin inhibitor currently available, mavacamten, is safe and effective in the initiating phase. Implementing mavacamten therapy requires *CYP2C19* genetic testing, frequent echocardiographic monitoring and dose adjustments to ensure patient safety. The challenge of non-responders to mavacamten is currently unresolved, and these patients will continue to require septal reduction therapies. Additionally, data on long-term safety and efficacy are necessary to determine mavacamten's place in the treatment cascade of oHCM.

Contributors SS and J-CR were involved in study conception and design. Data collection and analysis were performed by SS, CC and J-CR. All authors were involved in manuscript writing. The final manuscript version was approved by all authors. SS is the guarantor for this study and manuscript.

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Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Ethics Committee of Ruhr-Universität Bochum (AZ 2023-1019). Participants gave informed consent to participate in the study before taking part.

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Data availability statement Data are available upon reasonable request.

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REFERENCES

1 Ommen SR, Ho CY, Asif IM, *et al*. 2024 AHA/ACC/AMSSM/HRS/PACES/SCMR Guideline for the Management of Hypertrophic Cardiomyopathy: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *Circulation* 2024;149:e1239–311.
2 Arbelo E, Protonotarios A, Gimeno JR, *et al*. 2023 ESC Guidelines for the management of cardiomyopathies. *Eur Heart J* 2023;44:3503–626.
3 Maron MS, Olivotto I, Betocchi S, *et al*. Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. *N Engl J Med* 2003;348:295–303.
4 Green EM, Wakimoto H, Anderson RL, *et al*. A small-molecule inhibitor of sarcomere contractility suppresses hypertrophic cardiomyopathy in mice. *Science* 2016;351:617–21.
5 Olivotto I, Oreziak A, Barriales-Villa R, *et al*. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2020;396:759–69.
6 Desai MY, Owens A, Geske JB, *et al*. Myosin Inhibition in Patients With Obstructive Hypertrophic Cardiomyopathy Referred for Septal Reduction Therapy. *J Am Coll Cardiol* 2022;80:95–108.
7 CAMZYOS® Hartkapseln. 2024. Available: https://fi.b-ms.de/camzyos [Accessed 30 Sep 2024].
8 Available: https://www.ema.europa.eu/en/documents/product-information/camzyos-epar-product-information_en.pdf [Accessed 11 Nov 2024].
9 Ionova Y, Ashenhurst J, Zhan J, *et al*. CYP2C19 Allele Frequencies in Over 2.2 Million Direct-to-Consumer Genetics Research Participants and the Potential Implication for Prescriptions in a Large Health System. *Clinical Translational Sci* 2020;13:1298–306.
10 Ramonfaur D, Gasperetti A, Blake VE, *et al*. Eighteen-Month Real-World Experience Using Mavacamten for Treatment of Obstructive Hypertrophic Cardiomyopathy in a Racially Diverse Population. *JAHA* 2024;13.
11 Abood Z, Jan MF, Ashraf M, *et al*. Mavacamten in real-life practice: Initial experience at a hypertrophic cardiomyopathy centre. *ESC Heart Fail* 2025;12:672–6.
12 Kim DS, Chu EL, Keamy-Minor EE, *et al*. One-year real-world experience with mavacamten and its physiologic effects on obstructive hypertrophic cardiomyopathy. *Front Cardiovasc Med* 2024;11:1429230.
13 Desai MY, Hajj-Ali A, Rutkowski K, *et al*. Real-world experience with mavacamten in obstructive hypertrophic cardiomyopathy: Observations from a tertiary care center. *Prog Cardiovasc Dis* 2024;86:62–8.
14 Rader F, Oręziak A, Choudhury L, *et al*. Mavacamten Treatment for Symptomatic Obstructive Hypertrophic Cardiomyopathy: Interim Results From the MAVA-LTE Study, EXPLORER-LTE Cohort. *JACC Heart Fail* 2024;12:164–77.
15 Chuang C, Collibee S, Ashcraft L, *et al*. Discovery of Aficamten (CK-274), a Next-Generation Cardiac Myosin Inhibitor for the Treatment of Hypertrophic Cardiomyopathy. *J Med Chem* 2021;64:14142–52.
16 Maron MS, Masri A, Choudhury L, *et al*. Phase 2 Study of Aficamten in Patients With Obstructive Hypertrophic Cardiomyopathy. *J Am Coll Cardiol* 2023;81:34–45.
17 Coats CJ, Masri A, Nassif ME, *et al*. Dosing and Safety Profile of Aficamten in Symptomatic Obstructive Hypertrophic Cardiomyopathy: Results From SEQUOIA-HCM. *J Am Heart Assoc* 2024;13:e035993.