

Case Report

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Case Report

One-Year Real-World Experience with Mavacamten and its Physiologic Effects on Obstructive Hypertrophic Cardiomyopathy

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Abstract: We describe real-world use of mavacamten in 50 patients with oHCM. Consistent with EXPLORE-HCM and VALOR-HCM, we report significant improvement in wall thickness, mitral regurgitation, left ventricular outflow tract obstruction and NYHA class. Moreover, in our center's experience, neither arrhythmia burden, nor contractility have worsened in the vast majority of patients: We note a clinically insignificant mean decrease in left ventricular ejection fraction (LVEF), with only two patients requiring temporary mavacamten discontinuance for LVEF < 50%. Adverse events were rare, unrelated to mavacamten itself, and seen solely in patients with disease too advanced to have been represented in clinical trials. Our multidisciplinary pathway enabled us to provide a large number of patients with a novel closely-monitored therapeutic within just a few months of commercial availability. These data lead us to conclude that mavacamten, as a first-in-class cardiac myosin inhibitor, is safe and efficacious in real-world settings.

Keywords: mavacamten; cardiac myosin inhibitor; hypertrophic cardiomyopathy; heart failure

Hypertrophic cardiomyopathy is a genetic disease associated with variants in the genes of the cardiac sarcomere and characterized by enhanced cardiac actin-myosin crossbridge cycling leading to hyperdynamic contractility, cardiac hypertrophy, and diastolic dysfunction [1]. Obstructive hypertrophic cardiomyopathy (oHCM) occurs when hypercontractility, hypertrophy and mitral valve morphology contribute to outflow tract obstruction [1]. Mavacamten is a first-in-class, small molecule inhibitor of cardiac myosin ATPase approved by the US Food and Drug Administration in April 2022 for use in patients with symptomatic oHCM. Mavacamten reduces contractile force through decreased myosin head availability [2]. We now have more than 18 months of experience with commercial mavacamten following the Risk Evaluation and Mitigation Strategies (REMS) pathway, and no reports exist of its longer term, real-world effects. Here, we report a case series of



50 patients with oHCM treated with mavacamten and closely monitored through a multidisciplinary program at the Stanford Center for Inherited Cardiovascular Disease (SCICD).

Case report

A 26 year old man presented with severely reduced exercise capacity ($VO_{2\max}$ 67% of predicted) due to obstructive HCM characterized by severe septal hypertrophy (2.8 cm) with associated late gadolinium enhancement. He had normal-to-hyperdynamic left ventricular ejection fraction (LVEF, 63%) and a resting LVOT gradient of 90 mmHg with systolic anterior motion (SAM) of the mitral valve causing moderate mitral regurgitation. Genetic testing revealed a likely pathogenic variant in *MYH7* (c.1051A>G, p.Lys351Glu).

The patient developed decreasing exercise tolerance, with increasing left ventricular septal hypertrophy to 3.1cm (**Figure 1A**) and LVOT gradient of 112mmHg at rest (**Figure 1B**). His SAM-associated moderate mitral regurgitation worsened (**Figure 1C**). He had echocardiographic evidence of diastolic dysfunction, with reduced lateral e' of 3.9cm/s (**Figure 1D**). He deferred surgical myectomy out of concern for operative risk.

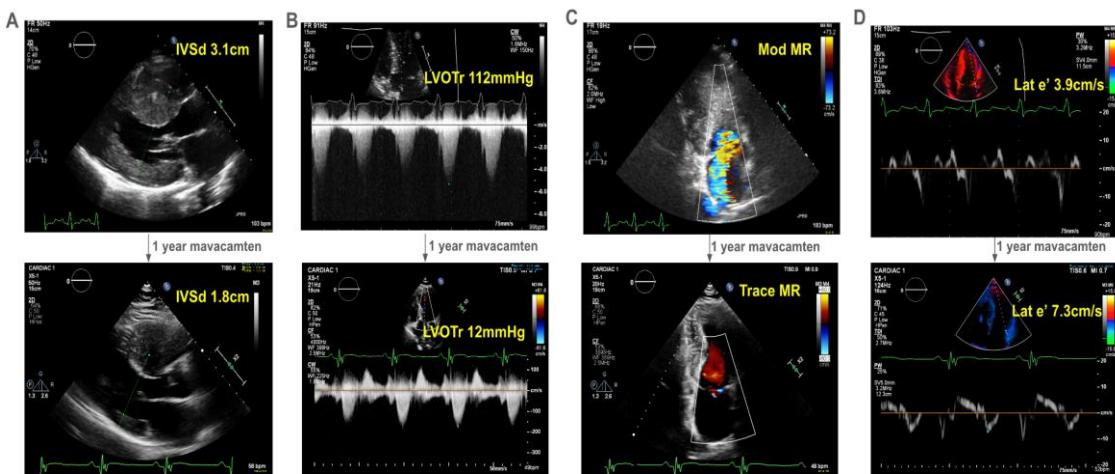


Figure 1. Echocardiographic changes after one-year of mavacamten in a 41-year old man with obstructive hypertrophic cardiomyopathy. With one-year of treatment with mavacamten, our proband experienced improved symptoms, which correlated echocardiographically (see online video) to A) a decrease in interventricular septum thickness on parasternal long axis view, B) his left ventricular outflow tract gradient at rest, C) the degree of mitral regurgitation, and D) his diastolic function as represented by his lateral e'. Abbreviations: IVSd - interventricular septum length in diastole in cm; LVOTr - left ventricular outflow tract gradient at rest in mmHg; MR - mitral regurgitation; lat e' - lateral e' in cm/s, a spectral doppler measurement reflecting diastolic function.

He started mavacamten at 40 years of age. After one year, there was dramatic improvement in his symptoms with a reduction in his interventricular septal thickness from 3.1cm to 1.8cm (**Figure 1A**) and resting LVOT gradient from 112 mmHg to 12mmHg (**Figure 1B**). Mitral regurgitation reduced to trace (**Figure 1C**). Finally, he had improvement in his lateral e' velocity from 3.9 cm/s to 7.3 cm/s (**Figure 1D, online video**).

One year experience of real world mavacamten therapy

We have observed similar trends across patients on mavacamten. In our cohort, 64% (32) were women with an average age of 63.5 ± 13.5 years (SD) and body-mass index of 28.5 ± 5.4 kg/m². All patients were closely monitored according to the FDA-mandated REMS pathway[3], with an average 36 weeks follow up. Mavacamten was temporarily held in 5 patients (10%) due to valsalva LVOT gradient <20mmHg, and in 2 patients (4%) for LVEF <50%[3]. Mavacamten was stopped in 3 patients (6%) for fatigue/malaise (n=2), and loss of insurance coverage (n=1). We noted minimal atrial fibrillation or non-sustained ventricular tachycardia on follow-up monitoring. Mavacamten doses on

most recent follow-up were: 2.5mg (9, 20%), 5mg (17, 38%), 10mg (13, 29%), and 15mg (6, 13%, **Table 1**).

Table 1. Baseline characteristics, clinical outcomes, and changes to echocardiographic data with mavacamten treatment in 50 patients with obstructive hypertrophic cardiomyopathy.

| Baseline Characteristics | | | |
|---|-----------------|---------------------------|--------|
| | N | Mean (\pm SD) or % (N) | P |
| Age, years | 50 | 63.5 (\pm 13.5) | - |
| Gender, % Female | 50 | 64.0% (32) | - |
| Body mass index, kg/m ² | 50 | 28.5 (\pm 5.4) | - |
| Clinical Outcomes with Mavacamten Treatment | | | |
| | N | Mean (\pm SD) or % (N) | P |
| Time in Mavacamten REMS, weeks | 45 | 35.9 (\pm 17.5) | - |
| Mavacamten temporarily held, % | 50 | 10.0% (5) | - |
| Mavacamten stopped, % | 50 | 6.0% (3) | - |
| New atrial fibrillation, % | 50 | 4.0% (2) | - |
| New ventricular tachycardia, % | 50 | 2.0% (1) | - |
| Death, MCS, or transplant, % | 50 | 6.0% (3) | - |
| | Baseline, % (N) | Post-Mavacamten, % (N) | P* |
| NYHA Symptom Classification | 49 | 43 | <0.001 |
| I - no limitations of activity | 0% (0) | 44.2% (19) | |
| II - slight limitations of activity | 30.6% (15) | 51.2% (22) | |
| III - marked limitations of activity | 69.4% (34) | 4.6% (2) | |
| IV - symptoms at rest | 0% (0) | 0% (0) | |

| Mavacamten dose at follow-up | 47 | 45 | - |
|---|-----------------|-------------------------------|--------|
| 2.5mg | - | 20.0% (9) | - |
| 5mg | - | 37.8% (17) | - |
| 10mg | - | 28.9% (13) | - |
| 15mg | - | 13.3% (6) | - |
| Change in Echocardiographic Data with Mavacamten Treatment | | | |
| | N | Mean Absolute Delta (95% CI)* | P** |
| LVOTr, mmHg | 37 | -33.1 (-45.3, -21.0) | <0.001 |
| LVOTv, mmHg | 32 | -50.1 (-68.5, -31.7) | <0.001 |
| LVEF | 42 | -3.1 (-5.4, -0.83) | 0.0088 |
| LV interventricular septum, cm | 42 | -0.22 (-0.30, -0.13) | <0.001 |
| E/e' | 19 | -4.0 (-9.7, 1.7) | 0.15 |
| Lateral e', cm/s | 18 | -0.53 (-1.9, 0.87) | 0.43 |
| Medial e', cm/s | 21 | -0.88 (-1.7, -0.087) | 0.032 |
| RVSP, mmHg | 23 | -2.5 (-5.6, 0.67) | 0.12 |
| | Baseline, % (N) | Post-Mavacamten, % (N) | P* |
| MR Severity | 47 | 39 | <0.001 |
| None/Trace | 14.9% (7) | 33.3% (13) | |
| Mild | 21.3% (10) | 51.3% (20) | |
| Moderate | 44.7% (21) | 12.8% (5) | |
| Moderately-Severe | 10.6% (5) | 2.6% (1) | |
| Severe | 8.5% (4) | 0% (0) | |

* McNemar-Bowker test used for calculation of P-value. ** Paired sample t-test used for calculation of P-value and 95% confidence intervals. Abbreviations: LV - left ventricle; LVEF - left ventricular ejection fraction; LVOTv - left ventricular outflow tract obstructive gradient with Valsalva maneuver; LVOTr - left ventricular outflow

tract obstructive gradient at rest; MCS - mechanical circulatory support; MR - mitral regurgitation; NYHA - New York Heart Association; RVSP - right ventricular systolic pressure; SD - standard deviation.

We observed significant changes in echocardiographic measurements of mavacamten-treated patients at most recent followup compared to baseline. In line with trial data, there was a dramatic mean decrease in LVOT gradient at rest and with Valsalva with reductions of -33mmHg [-45,-21] (95% CI) in resting LVOT gradient, and -51mmHg [-69,-32] reduction in Valsalva LVOT gradient ($P<0.001$, pairwise T-test.) There was significant improvement in the proportion of patients with moderate or severe mitral regurgitation ($P<0.001$, McNemar-Bowker, **Table 1**). Accompanying this change in LVOT gradient, we noted a significant decrease in diastolic interventricular septal thickness (-0.2 [-0.30, -0.13] cm, $P<0.001$, **Table 1**). We observed a clinically insignificant reduction in mean LVEF from 67 to 64% (-3.1 [-5.4,-0.8]%, $P=0.008$) without change in right ventricular systolic pressure ($P=0.12$, **Table 1**). There was a significant decrease in medial e' (-0.9 cm/s [-1.7, -0.09], $P=0.03$), but no significant change in E/e' or lateral e' (**Table 1**). These positive changes in echocardiographic measurements were mirrored by New York Heart Association (NYHA) symptom class, which improved dramatically with mavacamten treatment (McNemar-Bowker test, $P<0.001$). Two elderly patients with severe concomitant disease unrelated to oHCM (4%) died during follow up: One had pre-existing hypoxemic pulmonary hypertension that progressed. The second died from unrelated septic shock. One patient (2%) developed septic shock due to tricuspid valve endocarditis during which mavacamten was discontinued, and ultimately required ECMO and complex cardiac surgery. Only a limited subset of our cohort had pre- and post-mavacamten cardiopulmonary exercise stress testing ($n=7$), precluding meaningful statistical analysis.

To enable timely and optimally monitored access to cardiac myosin inhibitor therapy for our patients, our center developed a nurse-led training course for the FDA REMS program[3]. This training focuses on appropriate patient selection, prescription, authorization, triage and surveillance, and provides education on common clinical problems that can arise during therapy with an emphasis on interdisciplinary care. Particular emphasis was placed on REMS monitoring and dose adjustment based on echocardiographic parameters. In the hope that our experience can enable expert oHCM care with cardiac myosin inhibitors at other centers, our pathway and training tools are shared (see **online materials**).

Conclusions

We describe real-world use of mavacamten in 50 patients with oHCM. Consistent with EXPLORER-HCM[4] and VALOR-HCM[5], we report significant improvement in wall thickness, mitral regurgitation, LVOT obstruction and NYHA class. Moreover, in our center's experience, neither arrhythmia burden, nor contractility have worsened in the vast majority of patients: We note a clinically insignificant mean decrease in LVEF, with only two patients requiring temporary mavacamten discontinuance for LVEF < 50%. Adverse events were rare, unrelated to mavacamten itself, and seen solely in patients with disease too advanced to have been represented in clinical trials. Our multidisciplinary pathway enabled us to provide a large number of patients with a novel closely-monitored therapeutic within just a few months of commercial availability. These data lead us to conclude that mavacamten, as a first-in-class cardiac myosin inhibitor, is safe and efficacious in real-world settings.

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