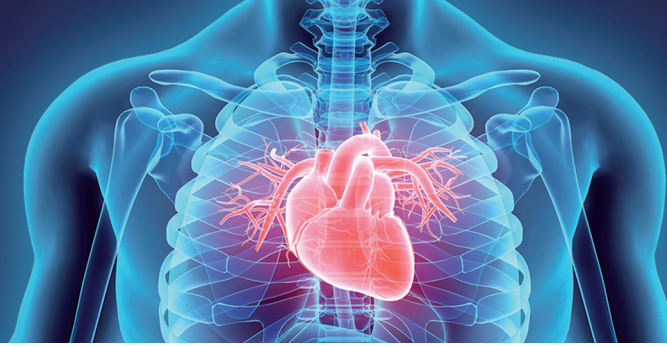
Heart Education USA

Journal Club 1 | April 2021



EXPLORER-HCM: Mavacamten improves exercise capacity and functional class in patients with obstructive hypertrophic cardiomyopathy (HCM)

During this Heart Education USA Journal Club, Dr Iacopo Olivotto, lead clinical investigator of the EXPLORER-HCM trial, and Dr Martin Maron, session Chair, discussed the effects mavacamten on exercise capability and functional class in patients with obstructive hypertrophic cardiomyopathy (HCM). After introducing the disease and available treatments, the trial results are presented. The experts discussed the most common symptoms in obstructive HCM before progressing to mavacamten's impact on the physiological effects of HCM and the mode of action. They then discussed how mavacamten may be integrated into the clinical management landscape, safe clinical practices, and potential regulatory approval.

Left ventricle outflow tract obstruction in HCM: a pathological conspiracy

Dr Olivotto opened by introducing the complexity and clinical consequences of HCM. He explained the complexity of the disease was not only about a thick heart, but that the pathophysiology of obstruction added a further degree of complexity. The hypertrophy of the left ventricle often narrows the outflow tract, misdirecting blood flow and capturing the mitral valve, which is then obstructed by the small cavity size. The mitral valves are elongated, and have abnormal papillary muscles, while the chords are short or absent. HCM is a hypercontractile condition favouring drag forces that pull the mitral valve to form a systolic anterior motion (SAM), while the left ventricular outflow tract (LVOT) dimensions are smaller compared to dimensions in non-HCM patients.

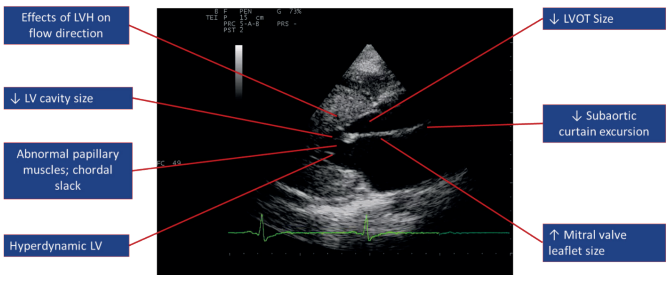


Figure 1. Echocardiogram image showing HCM physiological changes of the left ventricle
HCM: hypertrophic cardiomyopathy; LV: left ventricle; LVH: left ventricular hypertrophy; LVOT: left ventricular outflow tract

The treatment options available for symptomatic LVOT obstruction

Dr Olivotto states, in clinical practice, once HCM obstruction is symptomatic and the patient displays shortness of breath (dyspnoea), or angina, or atrial fibrillation, then the patient requires treatment. The first-line approach involves beta-blockers, non-dihydropyridine calcium antagonists (such as verapamil and diltiazem) and disopyramide. Disopyramide may be most effective because of the negative inotropic actions that weaken the force of muscular contraction.

If the drugs fail to relieve the symptoms, the "gold standard for refractory symptoms" is surgical myectomy. For patients not amenable to surgical myectomy, options include alcohol septal ablation, mitral valve clip, or dual-chamber pacing, although these treatments are applicable to a specific subset of patients and not considered the best options[1].

Treatment of obstruction HCM resistant to first-line therapy

A large-scale study in 2013[2] showed that 60% of patients with symptomatic HCM were unresponsive to beta-blockers or verapamil. (These patients received disopyramide, but 36% were also unresponsive to this drug.) Of the 40% who were drug responders, only 28% had adequate control of symptoms and LVOT gradients long term, and their final Minnesota Living with Heart failure Questionnaire classification was grade II. So, these were not asymptomatic patients, even at the trial end, although this was defined as satisfactory control with medical treatment. Dr Olivotto notes that in most cases of obstructive, symptomatic HCM, there are no drugs available to control symptoms satisfactorily. However, surgery has excellent results in controlling symptoms and the possibility to improve outcomes[3], but there are a world-wide lack of experienced surgeons.

Myosin inhibitors may counteract hypercontractivity

Myosin is overactive in HCM, although it is not clear whether it is a result of mutation in other sarcomere genes or within myosin genes. Many HCM mutations are on binding surfaces that destabilize the normal super-relaxed state of myosin[4]. Over-contraction results in too much energy consumption, while the hyper-contractile response may lead to energy profligate tissue ischemia, obstruction, and the long-term consequences of HCM.

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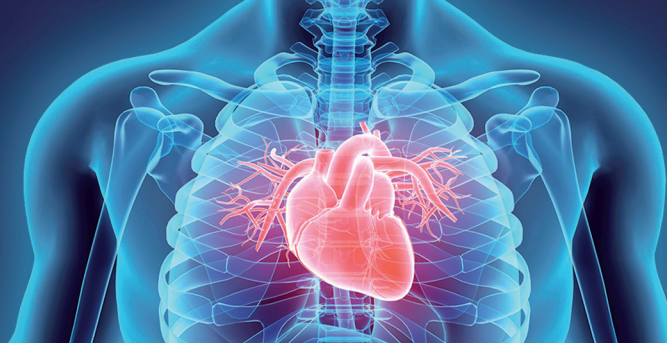

Mavacamten mode of action and the EXPLORER-HCM study

Mavacamten is a small molecule, first-in-class, cardiac myosin inhibitor developed to target the underlying cause of HCM by relaxing the actin-myosin cross-bridge and "tuning down the myosin and sarcomere system". Allosteric myosin inhibitors counter hypercontractivity and normalize the energetic and mechanical abnormalities. One of the core physiological mechanisms of HCM is caused by sarcomere protein gene mutations, changing the relaxed myosin state. The right side of figure 2 shows a typical HCM sarcomere with too many engaged cross-bridges (heads) involved in contraction at every single cycle. Mavacamten restores normality by reducing the number of heads involved in bridging between the actin filament and the myosin thick filament.

EXPLORER-HCM trial: study design and primary endpoints

The study[6] consisted of a double-blind phase III, multi-centre, randomised 1:1, placebo-controlled trial of 251 patients with New York Heart Association (NYHA) class I-II with an LVOT gradient ≥50mmHG. Patients received either once-daily oral mavacamten (N=123; 5mg with a 2 step-titration) or a placebo (N=28), in addition to their normal standard of care, for 30 weeks with a baseline and end of treatment assessment.

The primary endpoints were a hierarchical composite of minor, but good, symptomatic responses or a better peak volume of oxygen response (pVO2) with no worsening of NYHA class compared with baseline. The secondary endpoints were the change in assessments from baseline to week 30 in: post-exercise LVOT gradient change, pVO2, NYHA class, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score (KCCQ-CSS), and HCM Symptom Questionnaire-Shortness of Breath score (HCMSQ-SoB).

Mavacamten improved all four primary outcomes patients in comparison to patients receiving the placebo.

- For primary endpoint 1, where there was either ≥1.5 mL/kg per min increase in pVO2 with a ≥ 1 NYHA class improvement or ≥3.0 mL/kg per min increase in pVO2 with no worsening of NYHA class, more mavacamten patients showed an increase compared with placebo patients from baseline to 30 weeks (37% vs 17%, respectively: mean difference [95% confidence interval (CI)] 19.4% [8.7, 30.1]; P = 0.0005).
- For primary endpoint 2, where there was ≥1.5 mL/kg per min increase in pVO2 with a > 1 NYHA class improvement, more mavacamten patients showed an increase compared with placebo patients from baseline to 30 weeks (33% vs 14%, respectively: mean difference [95% CI] 19.3% [9.0, 29.6]).
- For primary endpoint 3, where there was ≥3.0 mL/kg per min increase in pVO2 with no worsening NYHA class, more mavacamten patients showed an increase compared with placebo patients from baseline to 30 weeks (24% vs 11%, respectively: mean difference [95% CI] 12.6% [3.4 ,21.9]).
- For primary endpoint 4, where there was ≥3.0 mL/kg per min increase in pVO2 with ≥ NYHA class improvement, more mavacamten patients showed an increase compared with placebo patients from baseline to 30 weeks (20% vs 0%, respectively: mean difference [95% CI] 12.5% [4.0 ,21.0]).

Dr Olivotto notes that 25% of mavacamten patients were double responders by achieving both primary endpoint definitions of ≥3.0 mL/kg per min pVO2 improvement and ≥ NYHA class improvement.

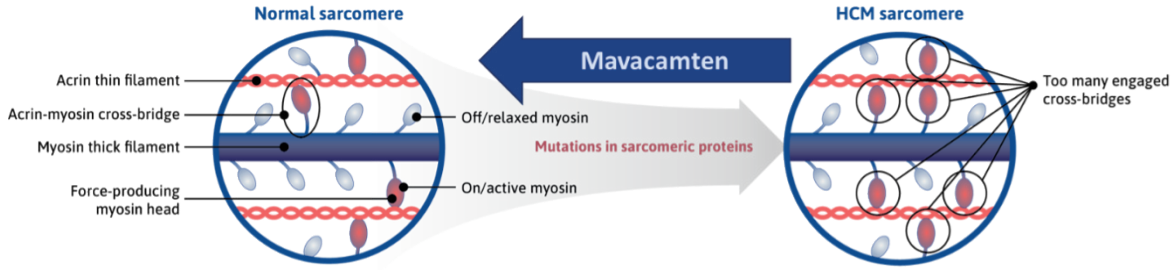

Figure 2. Mavacamten mode of action, showing the actin-myosin filament bridge. Adapted from Anderson et al (2018)[5].

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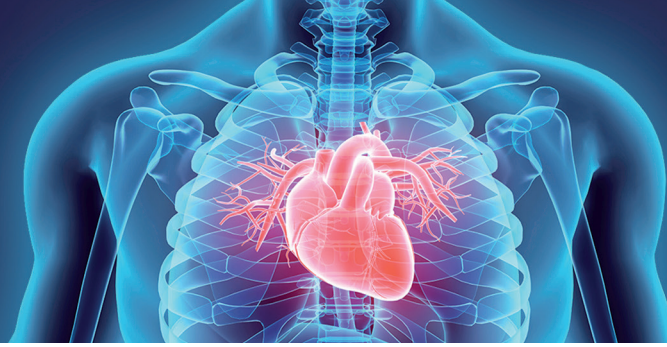

Mavacamten improves patient outcomes used for post-surgical assessment (secondary endpoints)

Mavacamten patients also showed improved secondary endpoints from baseline to week 30 in comparison to placebo patients. Dr Olivotto notes the secondary endpoints resemble the outcomes used for patient assessment after a successful surgical myectomy.

- Mavacamten patients showed a greater drop in post-exercise LVOT gradient compared with placebo patients (mean mmHg ± standard deviation (SD), -47 ± 40 vs -10 ± 30; difference between groups [95% CI], -36 [-43.2, -28.2]; P < 0.0001; upper left graph, figure 3).

Dr Olivotto notes the importance of the mavacamten group response as the drop to below 50mmHg takes them below the threshold indicated for surgical intervention.

- Mavacamten patients increased slightly from baseline pVO2 compared with placebo patients (mean mL/kg/min ± SD, 1.40 ± 3.1 vs 0.05 ± 3.0; difference between groups [95% CI], 1.35 [0.58, 2.12]; P = 0.0006).
- Mavacamten patients showed an improvement in NYHA class compared with placebo patients (% change, 35% vs 31.3; difference between groups [95% CI], 34% [22.2, 45.4]; P < 0.0001).
- Dr Olivotto highlighted that most patients were NYHA class II patients at baseline, therefore most mavacamten patients improved to class I.
- For the patient-reported, quality-of-life outcomes, both showed a clear effect of mavacamten.
- Mavacamten patients showed an improvement in KCCQ-CSS compared with placebo patients (mean ± SD, 13.6 ± 14.4 vs 4.2 ± 13.7; difference between groups [95% CI], 9.1 [5.5, 12.7]; P < 0.0001).
- Mavacamten patients also showed an improvement in HCMSQ-SoB compared with placebo patients (mean ± SD, -2.8 ± 2.7 vs -0.9 ± 2.4; difference between groups [95% CI], -1.8 [-2.4, -1.2]; P < 0.0001).

Dr Olivotto explains that most patients are most interested in feeling well, rather than having an interest in LVOT gradient changes, so the quality-of-life improvements were considered a very successful outcome.

Looking at the haemodynamic results, both the resting LVOT gradient and the Valsalva-procedure LVOT gradient show a fast, and sustained, drop in the mavacamten group compared with the placebo group (lower graphs, figure 3). The haemodynamic effect on left ventricle ejection fraction (LVEF) was slightly different between groups, with mavacamten showing a 4% drop, but the placebo group showing no change in systolic function over the 30-week trial (upper right graph, figure 3).

EXPLORER-HCM: LVOT gradients and LVEF over time

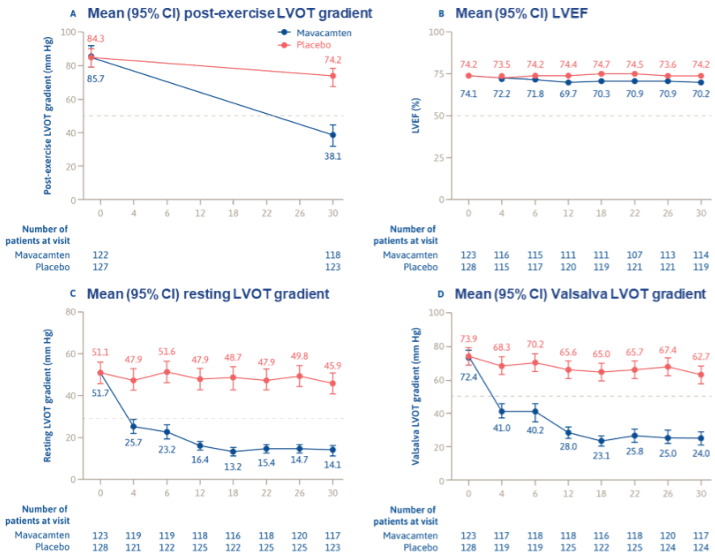

Figure 3. EXPLORER-HCM secondary outcomes

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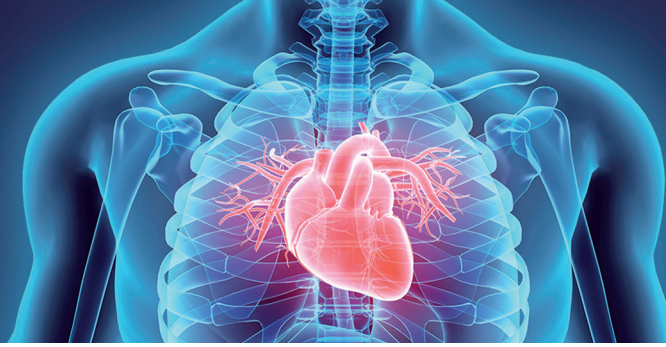

Mavacamten tolerability to patients

Dr Olivotto describes a low drop-out rate in this trial (2%; 3 mavacamten and 2 placebo), with no withdrawals due to reduced LVEF or symptoms of heart failure. Treatment-emergent adverse events, (defined as any event not present prior to the treatment or any already present that worsens following treatment) occurred in 87.8% of mavacamten patients and 78.9% of placebo patients. Serious adverse effects occurred in 8.1% of patients receiving mavacamten and 11% of patients receiving placebo, although a higher number of serious events occurred in the placebo group (20) vs the mavacamten group (12). Serious adverse cardiac events occurred in 4 patients in the mavacamten group and 4 patients in the placebo group. There was one sudden death in the placebo group. Atrial fibrillation events occurred in 6.5% of mavacamten patients verus 7.5% of placebo patients, while 4.6% of mavacamten patients experienced atrial fibrillation serious adverse events verus 3.1% of patients in the placebo group.

Dr Olivotto notes there were concerns for the safety of mavacamten since it was a first-in-class, negative inotrope, but the overall, treatment-emergent adverse event and serious adverse event profiles were similar in both the mavacamten and placebo groups. There was very high compliance of patients during the trial with a 97% completion rate. Dr Olivotto explained that two patients developed stress-related ballooning of the left ventricle in the mavacamten group (stress-related cardiomyopathy), although this complication was reversed, and investigations were underway as to the cause.

Conclusions

- Historically, drugs did not improve most cases of obstructive, symptomatic HCM. While surgery usually controls symptoms and may improve outcomes[3], there are too few experienced surgeons to meet demand.
- Mavacamten is a small molecule, first-in-class, cardiac myosin inhibitor.
- In the EXPLORER-HCM trial, mavacamten, compared with placebo, improved all four elements in the primary outcome composite of minor, but good, symptomatic responses or a better pVO2 with no worsening of NYHA class compared to baseline.
- Mavacamten also improved, compared with placebo, the secondary endpoints, which resemble the outcomes used to assess patients after surgical myectomy, namely changes from baseline to week 30 in: post-exercise LVOT gradient change, pVO2, NYHA class, KCCQ-CSS and HCMSQ-SoB. Importantly, mavacamten improved both quality-of-life outcome measures.
- Mavacamten was well tolerated. The dropout rate was low, with no withdrawals due to reduced LVEF or symptoms of heart failure. The causes of the reversible stress-related cardiomyopathy associated with mavacamten are being investigated.

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