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Review

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A New Chapter in the Management of Hypertrophic Cardiomyopathy: Cardiac Myosin Inhibitors

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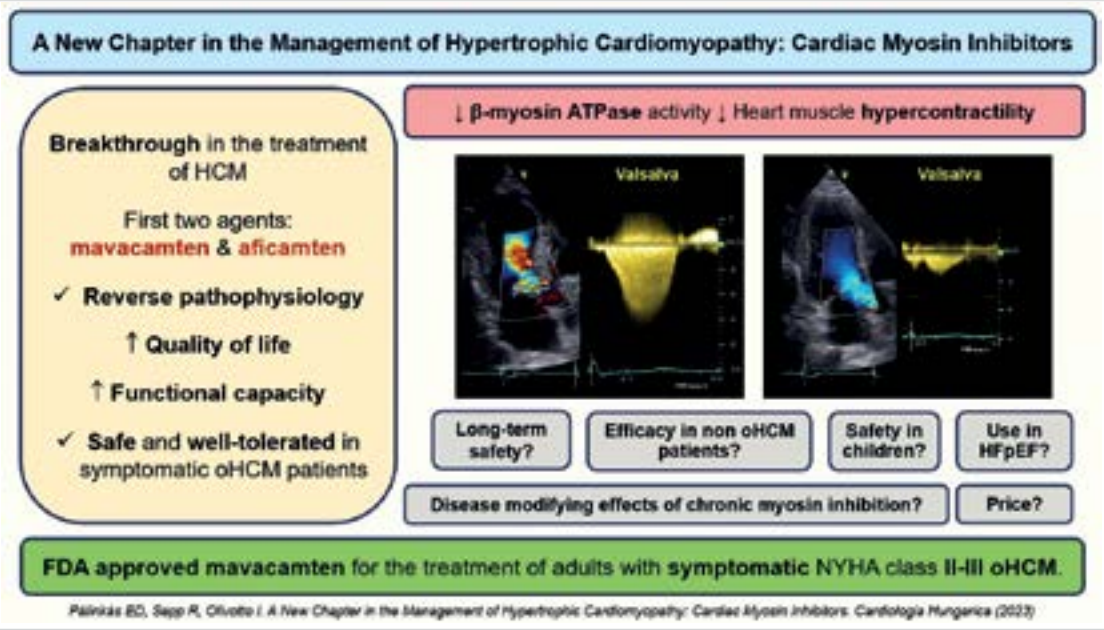
Video summary from the author

In the recent years, there has been a significant breakthrough in the treatment of hypertrophic cardiomyopathy. New precision molecules have been developed and successfully applied in clinical trials. A new class of orally available allosteric inhibitors reduces heart muscle hypercontractility, the core molecular defect of the disease, by selectively inhibiting cardiac beta-myosin. Based on the results obtained with the first two agents developed to date, mavacamten and aficamten, their use is safe and is associated with rapid and unprecedented improvement in quality of life and functional capacity in patients with left ventricular outflow tract obstruction, comparable to an optimal surgical result. This review provides an overview of the latest and most important studies that led to the approval of mavacamten by the U.S. Food and Drug Administration, and the clinical development of aficamten.

Keywords: hypertrophic cardiomyopathy, treatment, myosin inhibitors



GRAPHICAL ABSTRACT

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Hypertrophic cardiomyopathy (HCM) is a primary disease of the myocardium, usually caused by pathogenic mutations in genes encoding proteins of the cardiac sarcomere. Based on current screening techniques, it is now diagnosed more frequently and has an estimated prevalence of 1:200 globally (1, 2). Symptoms include shortness of breath, chest pain, exercise intolerance and fatigue, with a significant effect on the everyday life of patients. Typical disease-related complications comprise atrial fibrillation, recurrent ventricular arrhythmias, syncope, heart failure and sudden cardiac death (2). In HCM, genetic changes in cardiac sarcomere proteins promote myosin hyperactivation and excess adenosine triphosphate use, which results in excess myosin–actin cross-bridges during both systole and diastole, leading to inefficient hyperdynamic contraction and diastolic dysfunction (3, 4). In a group of HCM patients, these biochemical impairments, in combination with an abnormal left ventricular anatomy, mitral valvular apparatus and intraventricular hemodynamics, favor the systolic anterior motion of the mitral valve and induce an obstruction to blood flow, manifesting in a dynamic pressure gradient in the left ventricular outflow tract (LVOT) (5). Dynamic LVOT obstruction related to systolic anterior motion of the mitral valve is a well-known and distinctive hallmark of the disease. It is a primary driver of symptoms and exercise limitation and is an independent predictor of death, progression of heart failure and stroke in patients with HCM (6, 7). Current pharmacological management of LVOT obstruction concentrates on reducing symptoms by empiric use of beta-blockers, non-dihydropyridine calcium channel blockers, and disopyramide. However, these medications provide suboptimal relief of symptoms, have associated side effects, and do not target the core mechanism or modify the natural history of the disease (8). For patients refractory to medical management, septal myectomy or alcohol ablation may be an alternative to ameliorate symptoms. However, both procedures are invasive and require specialized care offered by only a few expert centers (9, 10). The extended knowledge of HCM pathophysiology in the last decades and the necessity for more efficient and less invasive treatments has led to the development of drugs that target the distinct mechanism of HCM.

Cardiac myosin inhibitors are precision molecules that selectively and reversibly inhibit the adenosine triphosphatase activity of cardiac beta-myosin, thus lessening hypercontractility, reducing sarcomere power and improving myocardial energetics in HCM (11). To date, mavacamten and aficamten are the two myosin inhibitors that have been developed and successfuly employed in clinical trials. Mavacamten is the first-in-class, allosteric myosin inhibitor approved by the U.S. Food and Drug Administration in April 2022. The approval was based on the groundbreaking phase III, EXPLORER-HCM trial (EXPLORER), which was a randomized, double-blind, placebo-controlled 30-week on-treatment trial of mavacamten in patients with obstructive HCM (oHCM) on standard background therapy, excluding disopyramide. The study revealed that patients who were administered mavacamten had a significant increase in mean peak oxygen consumption (pVO_2), a reduction in left ventricular outflow tract gradients (LVOTG) and a substantial improvement in physical function, symptoms and quality of life (12, 13). In detail, the trial fully met the primary endpoint: 37% of patients receiving mavacamten improved pVO_2 by 3.0 ml/kg per minute without worsening in New York Heart Association (NYHA) class or increased pVO_2 by 1.5 ml/kg per minute with at least one NYHA class reduction compared to 17% of patients on placebo. However, post hoc investigations revealed that the benefit of mavacamten treatment extends far beyond the measures of the primary endpoint. In particular, among those who did not reach the primary endpoint, 85% exhibited improvements in secondary/exploratory endpoints on mavacamten vs. 15% on placebo (14). Mavacamten significantly decreased LVOTG at rest, during Valsalva maneuver and after exercise (from 86 [95% CI: 80 to 92] to 38 [95% CI: 32 to 44] mmHg vs from 84 [95% CI: 78 to 91] to 73 [95% CI: 67 to 80] mmHg, mean intergroup difference [Δ]= −36 mmHg, [95% CI: −43 to −28 mmHg], p<0.0001), improved diastolic function (reduced lateral E/e' and left atrial volume index) and exercise capacity compared to placebo. Systolic anterior motion of the mitral valve disappeared in 81% of patients vs. 34% on placebo after 30 weeks (15). Mavacamten was associated with substantial improvements in physical function, symptom relief, and quality of life. 65% of patients had >1 NYHA class improvement, vs. 31% in the placebo group and approximately 75% of patients in NYHA II became asymptomatic on mavacamten. Additionally, 27% of patients on mavacamten achieved a complete response (rest, Valsalva and stress LVOTG <30 mmHg and NYHA class I, comparable to an optimal surgical result) compared to less than 1% receiving a placebo. The clinical and hemodynamic benefit was independent of age and gender and was associated with a marked reduction in serum N-terminal pro–B-type natriuretic peptide (NT-proBNP) and high sensitivity cardiac troponin I12,15. The favorable effects of mavacamten were confirmed by cardiac magnetic resonance imaging in a small sub-study of EXPLORER. The 30-week treatment reduced the absolute intracellular myocardial mass index (Δ= −13 g/m^2, [95% CI: −19 to −9 g/m^2], p<0.001), LV mass index (Δ= −16 g/m^2, [95% CI: −23 to −9 g/m^2], p<0.0001), left ventricular maximal wall thickness (Δ= –2 mm, [95% CI: −4 to −1 mm], p=0.008) and left atrial volume index (16). Longer-term observations ranging up to three years confirm the efficacy and safety of the drug *(Figure 1–3)* (17).

The recent VALOR-HCM trial (VALOR) directly investigated a more challenging endpoint, testing whether

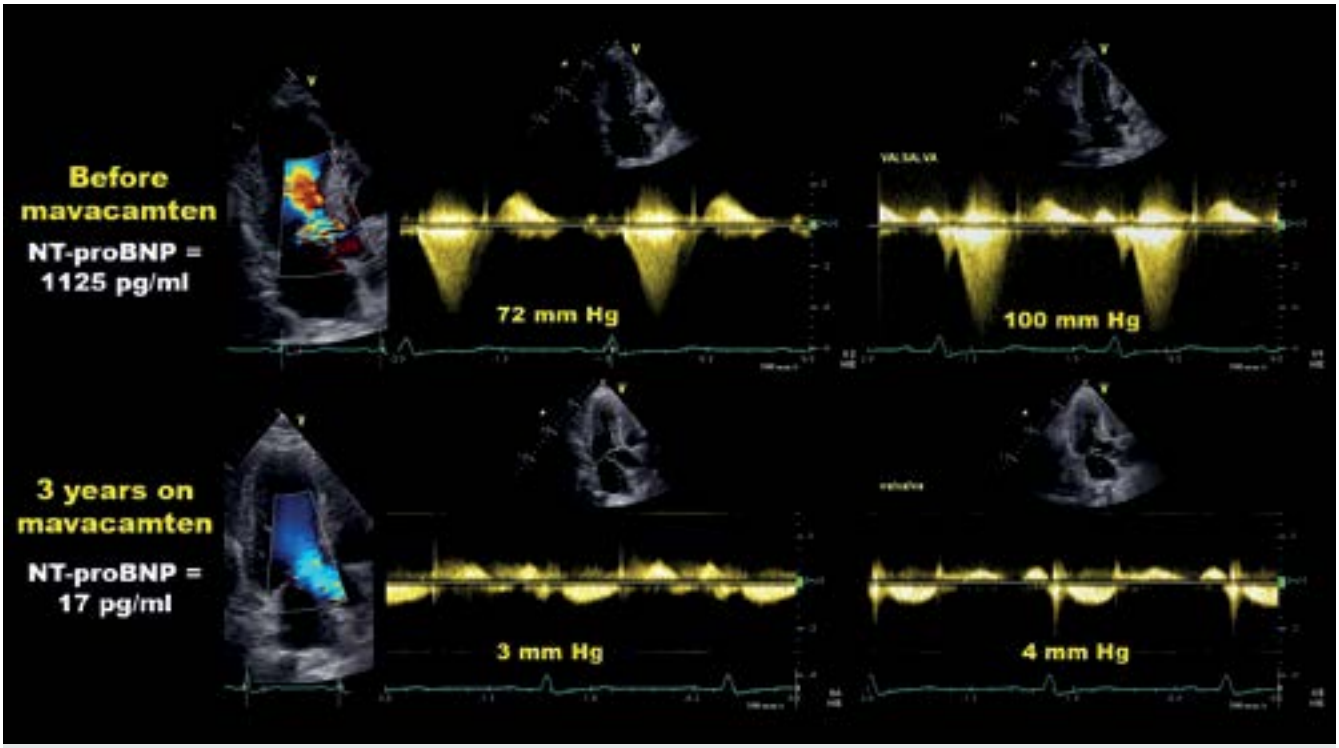

FIGURE 1. Effects of mavacamten on left ventricular outflow tract (LVOT) obstruction in obstructive hypertrophic cardiomyopathy. Upper panel: echocardiographic features at baseline in a sample subject, presenting with severe LVOT obstruction (resting 72 mmHg, Valsalva 100 mmHg) and left ventricular hypercontractility (left ventricular ejection fraction 75%). Lower panel: At the end of the third year of treatment with mavacamten, there is complete abolition of LVOT gradient (resting 3 mmHg, Valsalva 4 mmHg). N-terminal pro-B-type natriuretic peptide dropped from 1125 pg/ml at baseline to 17 pg/ml at end of follow-up

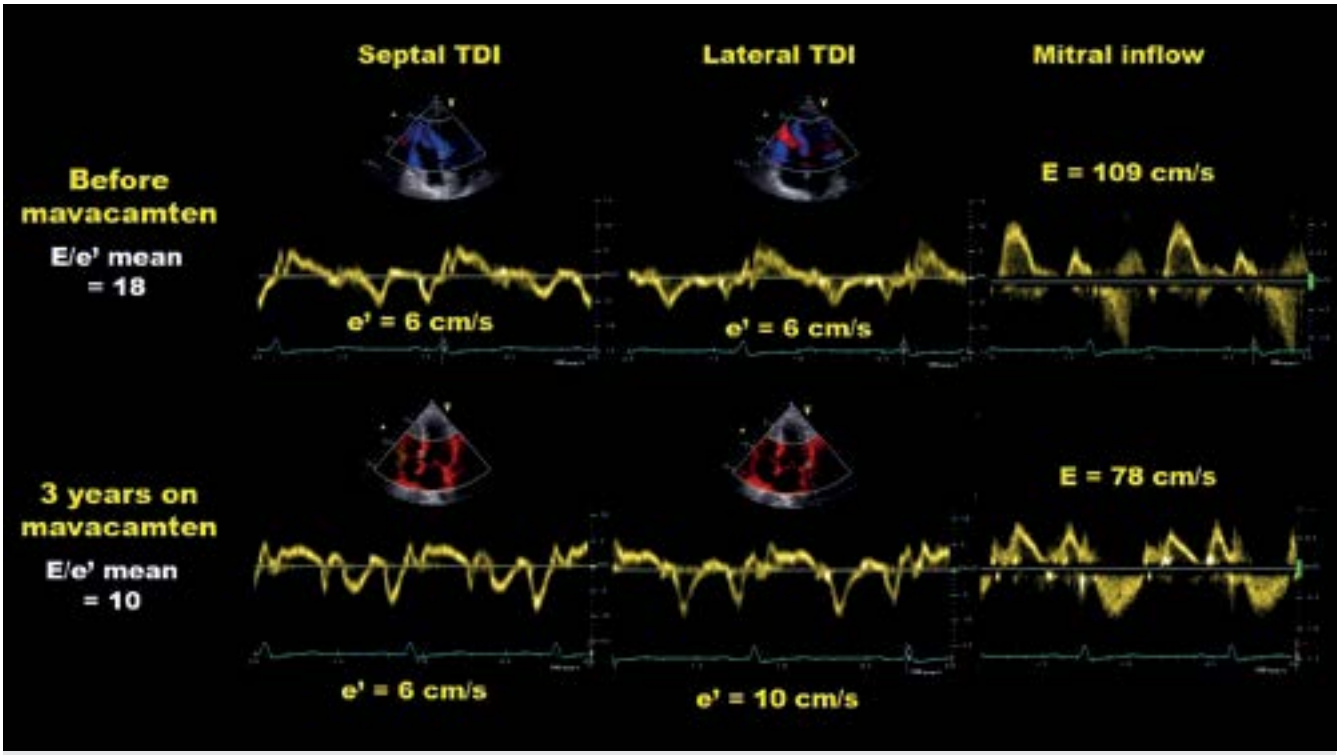

FIGURE 2. Effects of mavacamten on diastolic function in obstructive hypertrophic cardiomyopathy. Same subject as in Figure 1. E: early mitral inflow velocity; e': early diastolic mitral annular velocity; TDI: tissue Doppler imaging

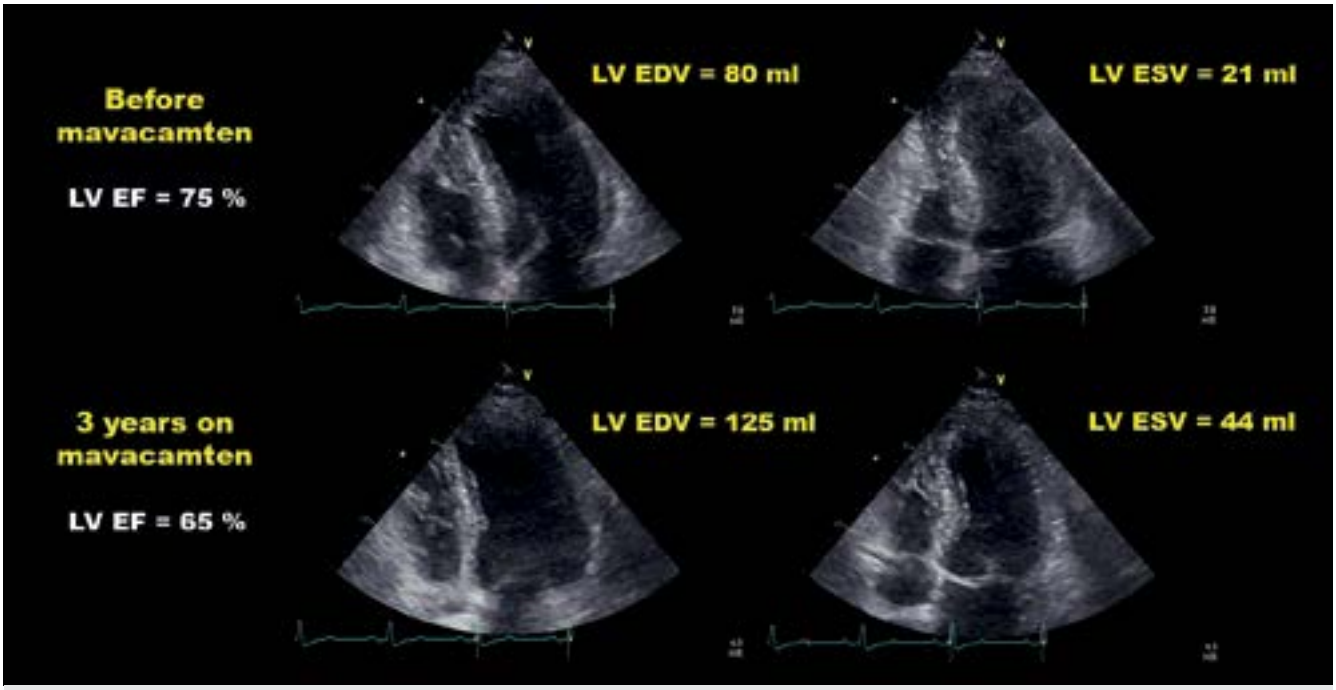

FIGURE 3. Effects of mavacamten on cardiac remodeling in obstructive hypertrophic cardiomyopathy. Same subject as in Figure 1. There is evident left- and right ventricular chamber remodeling and increase in volumes, with reduction in left ventricular ejection fraction (65%), still within the normal range. EDV: end-diastolic volume; EF: ejection fraction; ESV: end-systolic volume; LV: left ventricle

mavacamten may postpone or avoid the need for invasive myocardial reduction therapy in eligible patients according to the 2011 AHA/ACC guidelines (NYHA class III or IV or NYHA class II with exertion-induced syncope or near syncope, and a dynamic LVOTG at rest or with provocation >50 mmHg) (18). After 4 months of treatment with mavacamten, invasive septal reduction was no longer indicated in 82% of patients compared to 23% on placebo. In detail, 63% in the mavacamten group improved >1 NYHA class and 27% showed >2 NYHA class improvement compared to 21% and 2% in the placebo group, respectively. Mavacamten reduced resting (Δ= −33 mmHg, [95% CI: −42 to −25 mmHg], p<0.001), Valsalva (Δ= −48 mmHg, [95% CI: −58 to −37 mmHg], p<0.001) and exercise LVOTG (Δ= −37 mmHg, [95% CI: −48 to −26 mmHg], p<0.001) compared to placebo. Furthermore, among patients treated with mavacamten, 29% demonstrated improvement in diastolic function grade compared to 13% on placebo. Significant decrease occurred also in average E/e' ratio (–3+5 vs. 1+4, p <0.001) and indexed left atrial volumes (–5+8 vs. –1+8 ml/m^2, p=0.005) when compared to placebo. Consistent with EXPLORER, correlations between changes in diastolic indices (left atrial volume index, E/e' ratios) and changes in NT-proBNP were also noted. The findings of VALOR extend those of EXPLORER since:

1. a more symptomatic population was studied;
2. patients on disopyramide were also included;
3. mavacamten titration was based on echocardiography rather than pharmacokinetic parameters;
4. the left atrial volume index and average E/e' ratio improvement was independent of changes in LVOTG and mitral regurgitation;
5. changes in average E/e' ratio correlated with NYHA class and quality of life (19). After 8 months of treatment, 89% of patients were no longer candidates for invasive therapy, 90% improved ≥1 NYHA class and 30% showed ≥2 NYHA class improvement (20).

Mavacamten was tested also in nonobstructive HCM patients, in the rigorous, well-designed phase II, MAVERICK-HCM trial (21). Treatment with mavacamten was associated with a significant reduction in NT-proBNP and high-sensitivity cardiac troponin; however, the study was underpowered to detect clinical benefit. Regarding risks associated with the drug, a pooled analysis of currently available safety data from all phase II, phase III and long-term extension HCM studies, demonstrated that mavacamten is safe and generally well tolerated across multiple doses, regardless of the presence of obstruction (22). The most common undesired events were dizziness and fatigue in the pooled population and a similar proportion of patients receiving mavacamten and placebo experienced grade >3, serious emergent adverse events, largely unrelated to treatment (22).

Aficamten is the second in-class oral cardiac myosin inhibitor. It has similar mechanism of action as mavacamten, albeit it binds to a different allosteric location and reaches steady state more rapidly (23). It was recently evaluated in obstructive HCM in the phase

II REDWOOD-HCM trial, including 3 cohorts of patients (24). Symptomatic obstructive patients in Cohort 1 and 2 were randomly assigned to receive aficamten 5 mg titrated up to 15 mg (Cohort 1, n=14), aficamten 10 mg titrated up to 30 mg (Cohort 2, n=14) or placebo. Treatment with aficamten for 10 weeks resulted in a significant reduction in resting and provoked LVOT gradients, improved cardiac structure, mitral valve mechanics and myocardial relaxation with a concomitant reduction of NT-proBNP when compared to placebo (25, 26). Cohort 3 was an open-label study on obstructive HCM patients, symptomatic despite maximal therapy including disopyramide. The addition of 5, 10, and 15 mg of aficamten was well tolerated and provided a substantial decrease in resting and LVOT gradients also in Cohort 3, mirrored by a great improvement in HF symptoms in most patients, and a decrease in NT-proBNP (27).

Based on the recent, rapidly accumulating evidence, cardiac myosin inhibitors can reverse pathophysiology and ameliorate symptoms of HCM (17). Therefore, these successes constitute important proof that addressing specific molecular targets with agents developed on the basis of the scientific rationale, is the correct approach in genetic cardiomyopathies and will hopefully be followed by a host of similar initiatives in other conditions, as the efforts aimed at a definite cure by a genetic therapy still seems far away. Nevertheless, many gaps in knowledge remain: long-term safety, efficacy in nonobstructive HCM patients, disease-modifying properties of chronic myosin inhibition, safety in children, and importantly, a potential expansion of the indication to selected subsets of patients with heart failure with preserved ejection fraction. A relevant factor limiting a broad introduction of myosin inhibitors in clinical practice is likely represented by costs which for the only agent registered to date, mavacamten, reaches 90,000 Dollars/year in the U.S.A. Aficamten is still awaiting approval from the U.S. Food and Drug Administration, while mavacamten has been recently approved by the European Commission for the treatment of symptomatic adult obstructive HCM patients in all European Union member states (28). Despite these uncertainties, the future now looks brighter for patients with HCM.

Declaration of interest

IO has received grants and is a consultant for Bristol Myers Squibb and Cytokinetics. RS is a consultant for Bristol Myers Squibb. EDP has no conflict of interest to declare.

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