Mavacamten: treatment aspirations in hypertrophic cardiomyopathy

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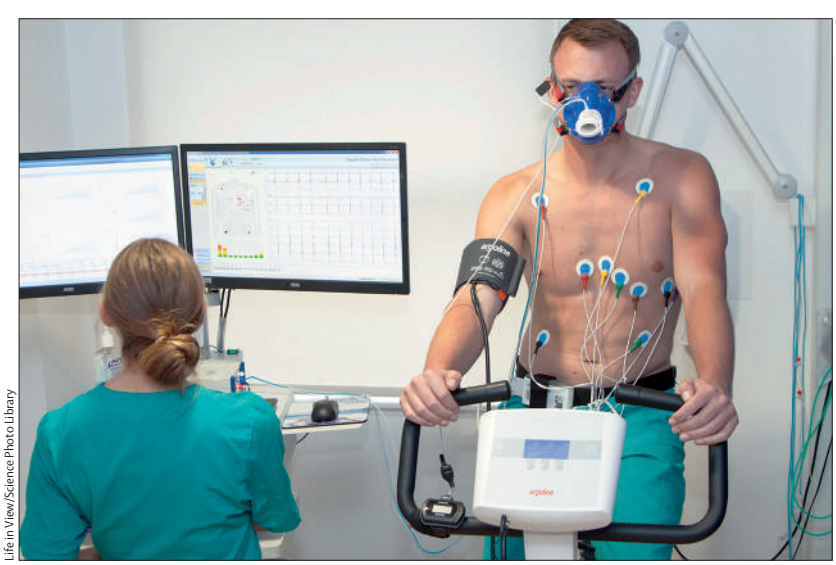
Managing dynamic left ventricular outflow tract (LVOT) obstruction remains one of the most challenging therapeutic aspects of hypertrophic cardiomyopathy. Individuals who are affected frequently present with disabling symptoms, which can be ameliorated following reduction of LVOT obstruction. Pharmacological treatment currently comprises non-disease specific therapies such as β blockers, negatively inotropic calcium channel blockers, and disopyramide, which offer a variable degree of symptomatic relief and are often limited by side-effects.[1] Enhanced myocardial contractility is a key factor in the pathophysiology of LVOT obstruction.[2] Mavacamten is a first-in-class, selective allosteric inhibitor of cardiac myosin ATPase, which reduces actin-myosin cross-bridge formation, thereby reducing myocardial contractility and improving myocardial energetics.[3] Animal studies showed that mavacamten reduced myocardial contraction in a dose-dependent manner and relieved LVOT obstruction.[4] These findings were replicated in a phase 2 trial (PIONEER-HCM), in which mavacamten reduced the post-exercise LVOT gradient, increased peak oxygen consumption (pVO_2), and improved symptoms in patients with the condition.[5]

In *The Lancet,* Iacopo Olivotto and colleagues report the EXPLORER-HCM trial, a phase 3, randomised-controlled trial that randomly assigned 251 patients (mean age 58·5 years; 41% women) with obstructive hypertrophic cardiomyopathy to either mavacamten or placebo.[6] Despite the multiple inclusion and exclusion criteria, the study population was generally representative of patients with obstructive hypertrophic cardiomyopathy who physicians are likely to encounter, making the results applicable to wider clinical practice. Importantly, the authors explored primary and secondary outcomes commonly used in clinical practice, such as shortness of breath and fatigue, functional capacity, LVOT gradient, and overall health status. After 30 weeks of treatment, mavacamten showed benefit across the spectrum, including the composite primary endpoint, its components, all secondary endpoints, patient-reported outcomes, and reductions in biomarkers of cardiac wall stress and myocardial injury. Specifically, compared with placebo, patients given mavacamten were more likely to reach the primary endpoint of pVO_2 and New York Heart Association (NYHA) class improvement (19·4%, 95% CI 8·7 to 30·1; p=0·0005), and showed greater reduction in post-exercise LVOT gradient (–36 mm Hg, –43·2 to –28·1; p<0·0001), had a greater increase in pVO_2 (1·4 mL/kg per min, 0·6 to 2·1; p=0·0006), and displayed improved patient-reported symptom scores (p<0·0001). Moreover, mavacamten induced a complete response, defined as NYHA class I and LVOT peak gradients less than 30 mm Hg (at rest, after Valsalva manoeuvre, or post exercise), in 27% of patients compared with only 1% in the placebo group. The effect of mavacamten on LVOT obstruction becomes more striking when we consider that the overwhelming majority (92%) of patients in the study were on background β blocker or calcium channel blocker therapy, agents which reduce the LVOT gradient. Moreover, it is well established that β blockers blunt heart rate response to exercise and therefore negatively affect pVO_2, which was part of the study's primary endpoint.

Encouragingly, the side-effect and safety profile did not differ between groups. A decrease in left ventricular ejection fraction to less than 50% was observed in seven (6%) patients on mavacamten, which resolved upon temporary discontinuation of treatment. There were no significant changes in heart rate and blood



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pressure from baseline to week 30, which is an important observation given that bradycardia and hypotension are limiting factors for escalating therapy with β blockers and calcium channel blockers.

The results of the EXPLORER-HCM trial should be interpreted with caution in patients who are not white and in younger populations, as these groups were under-represented in the study and should be included in future studies. In addition, the study provides no information relating to the concomitant use of disopyramide, which was included in the exclusion criteria, but is commonly used as a second-line therapy and can also prolong QT interval. Long-term follow-up data are required to assess the safety profile of mavacamten and whether its efficacy is sustained over time. A long-term extension study (MAVA-LTE, NCT03723655), which will treat all patients who completed the MAVERICK-HCM[7] and EXPLORER-HCM[6] studies with mavacamten, is in progress. Other avenues that are being explored include mavacamten as an alternative to septal reduction therapy (VALOR-HCM, NCT04349072). In the EXPLORER-HCM study, mavacamten reduced the peak LVOT gradient to less than the guideline-based threshold for septal reduction therapy (50 mm Hg) in 74% of patients, compared with 21% in the placebo group, indicating that mavacamten could represent a valid alternative to highly specialised invasive therapy. In addition, animal models showed that early administration of mavacamten halted the development of pathological ventricular hypertrophy and myocardial fibrosis and led to partial reversal of hypertrophy in older mice.[8] However, the wider application of mavacamten as a disease modifying therapeutic agent in hypertrophic cardiomyopathy remains to be proven.

Over the past six decades, few pharmacological studies have been completed in hypertrophic cardiomyopathy. Most have been small, with the majority comprising non-randomised cohorts with no long-term follow-up.[1] In the study of Olivotto and colleagues, treatment with mavacamten led to clinically meaningful improvements in haemodynamic status, functional capacity, and subjective wellbeing in patients with obstructive hypertrophic cardiomyopathy. Should mavacamten prove to be clinically effective and safe following long-term therapy in a larger and more diverse population, it would represent a much anticipated development in the treatment of hypertrophic cardiomyopathy. Were the drug to realise its potential as a disease modifying therapy in younger individuals, it would represent a great milestone in the area of inherited cardiomyopathies.

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Medical management of miscarriage with mifepristone

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Care of women with early pregnancy loss is changing for the better. The management of miscarriage dates back to at least 1843 with a curette invented by Recamier, which is now considered barbaric.[1] The rationale that, "Placental villosities are very frequently detected in utero after miscarriage…and their discovery points out the immediate cure of haemorrhage by removal of its inciting cause",[2] still holds true today. The goal of treatment of miscarriage is to efficiently and safely remove tissue from an early pregnancy loss to reduce haemorrhage and infection.

Unfortunately, miscarriage is common and stressful.[3] Both surgical and expectant management with spontaneous resolution have well established risks