`The end of the beginning for drug therapy in obstructive hypertrophic cardiomyopathy

Perry M Elliott
Professor of Cardiovascular Medicine, University College London

Short Title: Mavacamten in obstructive hypertrophic cardiomyopathy

Key Words: hypertrophic cardiomyopathy, mavacamten, cardiac myosin ATPase, outflow tract obstruction

Address for Correspondence

Professor Perry Elliott
Institute of Cardiovascular Science
University College London
Paul O'Gorman Building
72 Huntley St.
London WC1E 6AG
Tel: 020 7679 6500

Email: perry.elliott@ucl.ac.uk

Dynamic left ventricular outflow tract obstruction (LVOTO), a cardinal feature of hypertrophic cardiomyopathy (HCM), causes limiting symptoms and predisposes to adverse outcomes including atrial fibrillation and sudden cardiac death [1]. The essential constituent elements of LVOTO in HCM are narrowing of the left ventricular (LV) outflow tract caused by hypertrophy of the interventricular septum and systolic anterior motion of the mitral valve resulting in contact between the anterior leaflet and the thickened septum. LVOTO is typically increased by physiological manoeuvres that increase contractility, reduce LV volume, or decrease peripheral vascular resistance.

The association between LVOTO and LV hypertrophy inspired the first therapeutic intervention for the problem, surgical resection of the basal interventricular septum, but the risks of cardiac surgery, a lack of surgical experience, and the fact that many patients have complex cardiac anatomy that is unamenable to septal reduction, has spurred on the quest for alternative approaches. The sensitivity of LVOTO to the contractile state of the myocardium provides the rationale for the use of negative inotropic drugs–principally, ß-blockers, non-dihydropyridine calcium antagonists and disopyramide–to improve symptoms. Cumulative experience has shown that, in individual patients, drug therapy can be successful in reducing LVOTO, particularly in those with provocable or latent gradients, and clinical practice guidelines recommend medical therapy in symptomatic patients before invasive septal reduction therapy [2]. However, many patients continue to experience symptoms despite drug therapy or have to contend with barely tolerable side-effects. The recent publication of the EXPLORER-HCM trial, a randomised comparison of mavacamten against placebo in patients with obstructive HCM, opens a new chapter in the story of LVOTO management [3].

Targeting the fundamental pathophysiology of HCM

Cardiomyocytes consist of longitudinally arranged parallel myofibrils which are subdivided into contractile units called sarcomeres. Sarcomeres are the fundamental motor units of the cardiomyocyte and are made up of thin and thick myofilaments; the thick filament is made up of around 300 molecules of myosin, each composed of 2 protein units of β- or α-myosin heavy chain and 4 myosin light chain molecules; the thin filament is made up of repeating actin molecules, closely associated with the regulatory troponin

complex and α-tropomyosin. Another protein, cardiac myosin-binding protein C, contributes to the regulation of contraction.

Muscle contraction is caused by the sliding of thin filaments along thick filaments as the result of interaction between myosin and actin molecules. More precisely, with each contraction, the globular head of the myosin molecule bends towards and then binds to actin and then contracts, releases actin, and initiates a new cycle. This process is known as myosin-actin cycling and the links between the myosin head and actin are called cross-bridges. The movement of the myosin head requires the hydrolysis of ATP to release energy and is called the power stroke.

In around 40-50% of patients, HCM is caused by mutations in sarcomeric protein genes, the majority of which occur in β-cardiac myosin (*MYH7*) and cardiac myosin-binding protein-C (*MyBPC*). The earliest manifestations of HCM (before the development of hypertrophy) are impaired diastolic function with either preserved systolic function or hypercontractility and it is argued that it is hypercontractility which leads to hypertrophy, fibrosis, and myofilament disarray [4]. The molecular mechanisms that potentially explain this hypercontractile phenomenon include alterations in the actin-activated β-cardiac myosin chemo-mechanical ATPase cycle, an increased number of functionally accessible myosin heads, and alterations in load dependence contractility that change the power output of cardiac contraction.

The therapeutic potential of selective inhibition of cardiac myosin ATPase

Mavacamten is a novel selective allosteric inhibitor of cardiac myosin ATPase that restores the proportion of myosin in the super-relaxed state, thereby reducing the excess cross-bridges and normalizing ATP consumption [5]. Preclinical data from a murine model of HCM has shown that mavacamten reduces contractility, eliminates LVOTO and, if administered early, attenuates the development of ventricular hypertrophy [6]. In an open-label phase 2 clinical trial, PIONEER-HCM (NCT02842242), mavacamten reduced post-exercise LVOT gradients and improved exercise capacity and symptoms [7]. The most common adverse events were a dose-dependent reversible decrease in LV ejection fraction and atrial fibrillation.

The EXPLORER-HCM Trial

EXPLORER-HCM (NCT03470545) is a randomised, double-blind, placebo-controlled trial that enrolled patients with HCM and an LVOT gradient of ≥50 mm Hg and New York Heart Association (NYHA) class II–III symptoms [2]. Patients were assigned (1:1) to mavacamten or placebo for 30 weeks and the primary endpoint was a 1.5 mL/kg per min or greater increase in peak oxygen consumption (pVO2) during exercise and at least one NYHA class reduction or a 3.0 mL/kg per min or greater pVO2 increase without NYHA class worsening. Secondary endpoints included post-exercise LVOT gradient, pVO2, NYHA class, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score (KCCQ-CSS), and Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness-of-Breath subscore (HCMSQ-SoB).

Two hundred and fifty one patients were randomly assigned to mavacamten or placebo. Mavacamten reduced LVOT gradients and improved symptoms, exercise performance, and health status with consistent findings across all secondary endpoints. A complete response, defined as a reduction in LVOT gradient to less than 30 mm Hg and attainment of NYHA class I, was observed in 27% of patients receiving mavacamten compared to less than 1% of patients on placebo. Safety and tolerability were similar to placebo and treatment-emergent adverse events were generally mild. Only one patient died from sudden death in the placebo group.

Notable observations from the trial that might influence the clinical application of mavacamten and other similar agents include the following:

a) Interaction with ß-blockers

EXPLORER-HCM did not directly compare mavacamten with other drugs but did stratify the analysis by ß-blocker therapy. A higher proportion of patients not receiving ß-blockers reached the primary end-point (52.6% versus 8.7%) but there was no interaction with improvements in NYHA class or in submaximal gas exchange parameters during exercise. This probably reflects the constraint on cardiac output (and thus oxygen consumption) associated with ß-blockers but also suggests that mavacamten may be superior to ß-blocker therapy in treating symptomatic LVOTO.

b) Effect of mavacamten on left ventricular ejection fraction

The reduction in LVOTO was evident from week 4 and persisted throughout the 30 week period; in contrast, LV ejection fraction barely altered throughout the study (<5% in the treatment arm). Given the mechanism of action of mavacamten, this seems counterintuitive, but a similar phenomenon is reported with disopyramide and might reflect the reduction in mitral regurgitation that accompanies relief of LVOTO and which might increase stroke volume [8]. Only nine patients (seven on mavacamten and two on placebo) had reversible decreases in LVEF to less than 50%; of note, two patients developed 'stress cardiomyopathy' or takotsubo syndrome. This phenomenon is described in HCM, but two such episodes in a relatively small cohort seems excessive and warrants further investigation.

c) Impact of genotype on response to therapy

Although the inspiration for the development of mavacamten was the hypercontractile phenomenon observed with particular missense *MYH7* mutations, genotype was not a consideration for study inclusion in either the phase 2 PIONEER study or in EXPLORER-HCM. The subgroup analysis shows that patients with a positive genotype responded better than those without an identifiable mutation. Obviously, the impact of other confounders will need to be examined, but this observation raises the possibility that mutation negative patients may be less responsive.

Implications of EXPLORER-HCM

One of the most important lessons from EXPLORER-HCM is that randomised drug trials in HCM are not only feasible, but that they can also generate clinically meaningful findings with the potential to change medical practice. The strengths of EXPLORER-HCM include its statistical power (largest ever randomised clinical trial in HCM), the fact that the study cohort is representative of real World patients, and its use of clinically meaningful end-points. Weaknesses include a lack of a direct comparison with current standard of care and the need for a complex titration protocol that could be difficult to translate into clinical practice.

The findings in EXPLORER-HCM are promising, but the trial also reminds us that there is no panacea for the treatment of LVOTO. While contractility and loading conditions influence LVOTO, it is important to remember that it results from structural abnormalities that alter the relation of the MV to the LV outflow stream. Pharmacological therapy can reduce the force that drives the mitral leaflet forwards during systole, but it cannot correct the anatomical abnormality and so there will always be clinical scenarios in which drug therapy will be ineffective.

The discovery of mavacamten has renewed interest in the molecular consequences of HCM related sarcomere gene mutations and their potential as therapeutic targets. New studies are showing that mavacamten affects different aspects of the myosin chemomechanical cycle beyond the decrease of phosphate release from ß-cardiac myosin-S1; for example, a secondary decrease in the number of actin-binding heads transitioning from the weakly to the strongly bound state [9] and stabilisation of the sequestered, super relaxed state (SRX) of the protein with very slow ATP hydrolysis [10]. An important aspect of EXPLORER-HCM is its agnosticism with respect to the presence of and type of genetic mutation. A recent study has examined the effect of mavacamten in models of human troponin T and I mutations and has shown that the drug partially reversed pathological increases in calcium sensitivity, but incompletely rescued the contractile cellular phenotype and, in some cases, exacerbated the effect of the mutation [12]. Taken in the round, EXPLORER-HCM represents a major advance in the care of patients with the obstructive form of the disease, but we should proceed with caution, remembering that HCM represents a diverse range of different diseases and that one treatment is unlikely to fit all scenarios.

Conflicts of Interest

Principal investigator in EXPLORER-HCM. Recipient of consultancy fees from MyoKardia, Pfizer, Alynlam, Cytokinetics

References

1. Elliott P, McKenna WJ. Hypertrophic cardiomyopathy. Lancet 2004;363(9424):1881-91

2. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Authors/Task Force members, Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, Hagege AA, Lafont A, Limongelli G, Mahrholdt H, McKenna WJ, Mogensen J, Nihoyannopoulos P, Nistri S, Pieper PG, Pieske B, Rapezzi C, Rutten FH, Tillmanns C, Watkins H. Eur Heart J. 2014;35(39)s:2733-79.

3. Olivotto I, Oreziak A, Barriales-Villa R, Abraham TP, Masri A, Garcia-Pavia P, Saberi S, Lakdawala NK, Wheeler MT, Owens A, Kubanek M, Wojakowski W, Jensen MK, Gimeno-Blanes J, Afshar K, Myers J, Hegde SM, Solomon SD, Sehnert AJ, Zhang D, Li W, Bhattacharya M, Edelberg JM, Waldman CB, Lester SJ, Wang A, Ho CY, Jacoby D; EXPLORER-HCM study investigators. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2020:S0140-6736(20)31792-X. doi: 10.1016/S0140-6736(20)31792-X. Online ahead of print.

4. James A. Spudich. Three perspectives on the molecular basis of hypercontractility caused by hypertrophic cardiomyopathy mutations. Pflügers Archiv - European Journal of Physiology 2019; 471:701–717

5. Anderson RL, Trivedi DV, Sarkar SS, Henze M, Ma W, Gong H, Rogers CS, Gorham JM, Wong FL, Morck MM, Seidman JG, Ruppel KM, Irving TC, Cooke R, Green EM, Spudich JA. Deciphering the super relaxed state of human β-cardiac myosin and the mode of action of mavacamten from myosin molecules to muscle fibers. Proc Natl Acad Sci U S A. 2018;115(35):E8143-E8152

6. Green EM, Wakimoto H, Anderson RL, Evanchik MJ, Gorham JM, Harrison BC, Henze M, Kawas R, Oslob JD, Rodriguez HM, Song Y, Wan W, Leinwand LA, Spudich JA, McDowell RS, Seidman JG, Seidman CE.A small-molecule inhibitor of sarcomere contractility suppresses hypertrophic cardiomyopathy in mice. Science. 2016;351(6273):617-21

7. Heitner SB, Jacoby D, Lester SJ, et al. Mavacamten Treatment for Obstructive Hypertrophic Cardiomyopathy: A Clinical Trial. *Ann Intern Med*. 2019;170 (11):741-748.

8. Pollick C, Kimball B, Henderson M, Wigle ED. Disopyramide in hypertrophic cardiomyopathy. I. Hemodynamic assessment after intravenous administration. Am J Cardiol. 1988;62(17):1248-51

9. Kawas RF, Anderson RL, Ingle SRB, Song Y, Sran AS, Rodriguez HM. A small-molecule modulator of cardiac myosin acts on multiple stages of the myosin chemomechanical cycle. *J Biol Chem*. 2017;292(40):16571-16577. doi:10.1074/jbc.M117.776815

10. Sparrow AJ, Watkins H, Daniels MJ, Redwood C, Robinson P. Mavacamten rescues increased myofilament calcium sensitivity and dysregulation of Ca^{2+} flux caused by thin filament hypertrophic cardiomyopathy mutations. *Am J Physiol Heart Circ Physiol*. 2020;318(3):H715-H722.

Biographical Sketch

Personal photograph (figure 2)

Perry Elliott (H-index 104) is Professor of Cardiovascular Medicine at University College London (UCL) and a Senior Investigator of the UK National Institute for Health Research (NIHR). He is director of the UCL Centre for Heart Muscle Disease, Head of Clinical Research at the Institute of Cardiovascular Science UCL and a consultant cardiologist at St. Bartholomew's Hospital London, UK. He is Chairman of the ESC Heart Academy and the ESC Council on Cardiovascular Genomics, and past Chairman of the ESC Working Group on Myocardial and Pericardial Diseases (2010–2012) and the Executive Committee for the European Outcomes Research Programme registry on cardiomyopathies. He chaired the ESC Guideline Task Force on Hypertrophic Cardiomyopathy in 2014. He is President of Cardiomyopathy UK, Europe's foremost charity for patients with heart muscle disease and an executive Editor for the European Heart Journal. Over the past 25 years, Prof. Elliott has established an international reputation in the field of heart muscle disease, authoring more than 500 peer-reviewed papers on the subject. He develops diagnostic standards, risk stratification tools and clinical service models based on some of Europe's largest inherited heart disease cohorts, fostering multicentre research partnerships.

Figure Legends

Figure 1: Change in LVOT gradient, LVEF, and cardiac biomarkers

(From reference 4)

Mean post-exercise LVOT gradient over time (A), LVEF (B), resting LVOT gradient (C), and Valsalva LVOT gradient (D). Geometric mean over time is shown for NT-proBNP (E) and hs-cTnI (F). Error bars are 95% CIs. The dashed lines represent the threshold for guideline-based invasive intervention (LVOT gradient >50 mm Hg) in A and D, the threshold for guideline-based diagnosis of obstruction (LVOT gradient <30 mm Hg) in C, and the protocol threshold for temporary discontinuation (LVEF <50%) in B. hs-cTnI=high-sensitivity cardiac troponin I. LVEF=left ventricular ejection fraction. LVOT=left ventricular outflow tract. NT-proBNP=N-terminal pro B-type natriuretic peptide

Figure 2

Personal photograph

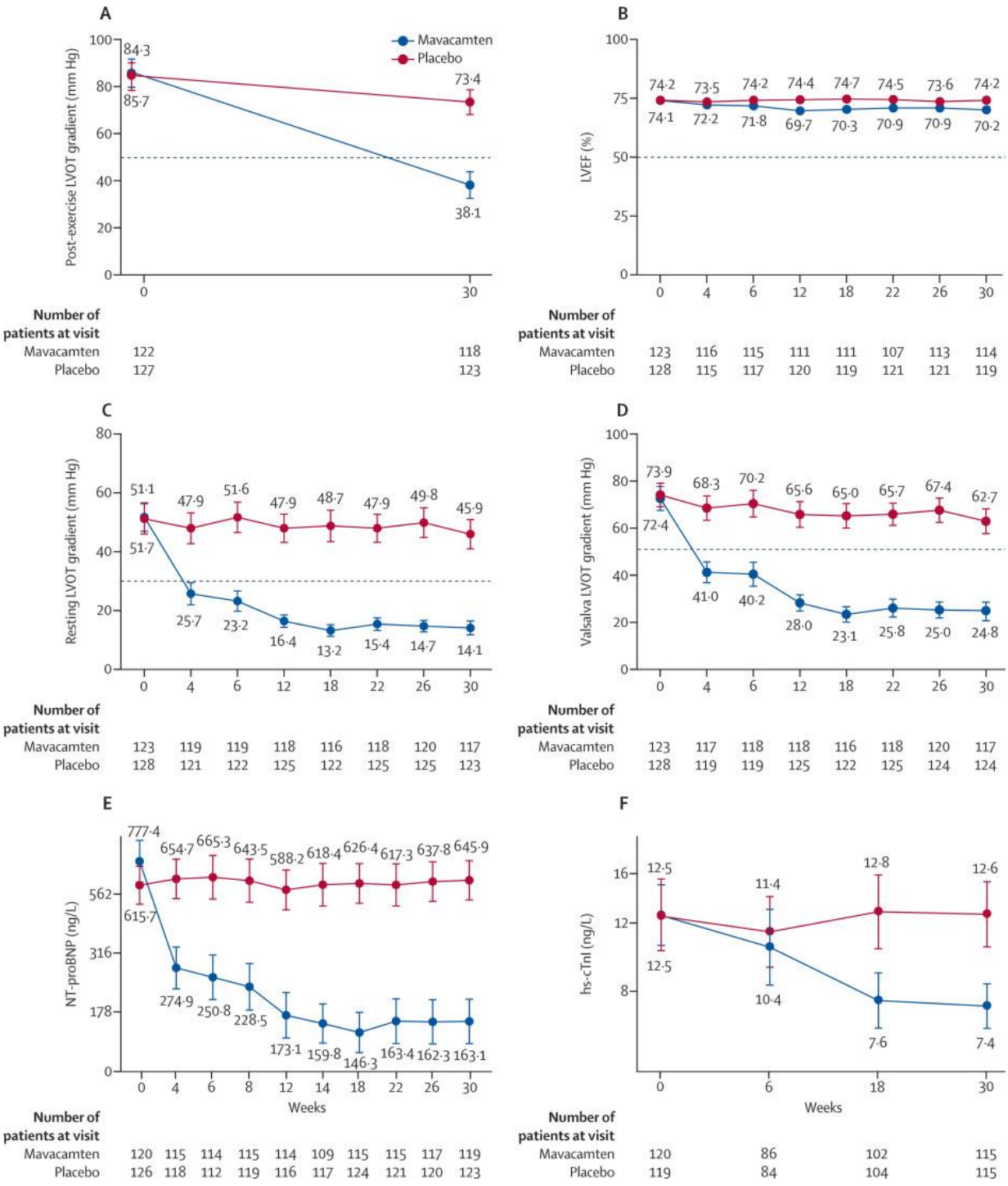
A
Mavacamten
Placebo
Post-exercise LVOT gradient (mm Hg)
84·3
85·7
73·4
38·1
Number of patients at visit
Mavacamten 122 118
Placebo 127 123
B
LVEF (%)
74·2 73·5 74·2 74·4 74·7 74·5 73·6 74·2
74·1 72·2 71·8 69·7 70·3 70·9 70·9 70·2
Number of patients at visit
Mavacamten 123 116 115 111 111 107 113 114
Placebo 128 115 117 120 119 121 121 119
C
Resting LVOT gradient (mm Hg)
51·1 47·9 51·6 47·9 48·7 47·9 49·8 45·9
51·7 25·7 23·2 16·4 13·2 15·4 14·7 14·1
Number of patients at visit
Mavacamten 123 119 119 118 116 118 120 117
Placebo 128 121 122 125 122 125 125 123
D
Valsalva LVOT gradient (mm Hg)
73·9 68·3 70·2 65·6 65·0 65·7 67·4 62·7
72·4 41·0 40·2 28·0 23·1 25·8 25·0 24·8
Number of patients at visit
Mavacamten 123 117 118 118 116 118 120 117
Placebo 128 119 119 125 122 125 124 124
E
NT-proBNP (ng/L)
777·4 654·7 665·3 643·5 588·2 618·4 626·4 617·3 637·8 645·9
615·7 274·9 250·8 228·5 173·1 159·8 146·3 163·4 162·3 163·1
Weeks
Number of patients at visit
Mavacamten 120 115 114 115 114 109 115 115 117 119
Placebo 126 118 112 119 116 117 124 121 120 123
F
hs-cTnI (ng/L)
12·5 11·4 12·8 12·6
12·5 10·4 7·6 7·4
Weeks
Number of patients at visit
Mavacamten 120 86 102 115
Placebo 119 84 104 115

Figure 1

Figure 2: