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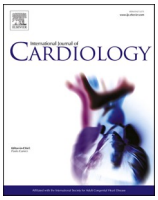

Mavacamten effectively reduces > 100 mmHg left ventricular outflow tract gradients as early as one week of treatment in obstructive hypertrophic cardiomyopathy

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ABSTRACT

Background: Real-world data on the efficacy of mavacamten, indicated for the treatment of obstructive hypertrophic cardiomyopathy (oHCM), are relatively scarce, particularly in patients with extreme left ventricular outflow tract (LVOT) gradients and concerning its short-term effects.

Patients/Methods: We investigated a cohort of twenty-five oHCM patients [15 men (60 %), mean age: 55 ± 11 years], with a resting or provoked LVOT gradient of >100 mmHg, receiving mavacamten treatment. Patients underwent a complete standard and 2D-speckle tracking echocardiographic examination after one week (W1) of treatment initiation and at subsequent four-week intervals.

Results: After only one week of mavacamten therapy, both the resting peak LVOT gradient (from 121 to 87 mmHg) and the Valsalva gradient (from 167 to 129 mmHg) significantly decreased (all $p < 0.001$), showing further decrease (resting gradient: to 67 mmHg at W4, and to 56 mmHg at W8; Valsalva gradient to 102 mmHg at W4, and to 80 mmHg at W8, all $p < 0.001$). NTproBNP levels also significantly decreased already at W1 (−1467 pg/ml), showing further decrease during treatment (−1735 pg/ml at W4, and − 2048 pg/ml at W8; all $p <$ 0.001). NYHA functional class, 6-min walk distance, parameters of myocardial work and many of the assessed diastolic parameters showed significant improvements and no change in LV ejection fraction or global longitudinal strain was observed.

Conclusions: Mavacamten effectively reduced even >100 mmHg LVOT gradients and led to significant gradient reduction already in one week. Besides favourable changes in LVOT obstruction, structural and functional echocardiographic parameters, functional capacity, and cardiac biomarkers, it also led to significant improvement in myocardial work parameters.

1. Introduction

The selective and reversible cardiac myosin inhibitor mavacamten was developed for the treatment of hypertrophic cardiomyopathy (HCM) [1], the most common heritable heart muscle disease. By modulating the number of available myosin heads mavacamten promotes an energy-sparing, super-relaxed state of the myosin molecule, thereby reducing the force-producing systolic and residual diastolic cross-bridge formation [2,3].

The clinical efficacy of mavacamten was evaluated in the

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EXPLORER-HCM [4] and VALOR-HCM [5] clinical trials which proved the beneficial effects of mavacamten. The EXPLORER-HCM trial showed in 251 symptomatic adult patients with obstructive HCM (oHCM) that a larger proportion of patients met the primary endpoint of the study comprising a change at week 30 in exercise capacity (measured by pVO2) and symptoms (measured by NYHA functional classification). Mavacamten treatment was also associated with a significant improvement in all secondary endpoints, including reduced LVOT gradient, increased pVO2, and improved symptoms. Decreases in cardiac biomarker levels were similarly rapid and sustained while changes in baseline systolic function associated with mavacamten were small. In the VALOR trial mavacamten was shown to be superior in meeting the primary composite endpoint at week 16 which was a composite of patient decision to proceed with septal reduction therapy (SRT) or patients who remain SRT eligible (LVOT gradient of ≥50 mmHg and NYHA class III-IV, or class II with exertional syncope or near syncope). Long term extension studies revealed that treatment with mavacamten over 180 (EXPLORER-HCM) [6] and 128 weeks (VALOR-HCM) [7] showed a sustained decrease in resting and Valsalva LVOT gradients, NT-proBNP levels, as well as improvements in NYHA class.

Based on these landmark trials, mavacamten was approved for clinical use [8,9]. In addition to regulatory approval, the 2023 Guidelines for the management of cardiomyopathies by the ESC [10] and the 2024 Guideline for the management of hypertrophic cardiomyopathy by the AHA/ACC [11] introduced recommendations for the use of mavacamten as a second-line therapy for oHCM, in addition to a beta-blocker or non-dihydropyridine calcium channel blockers to improve symptoms in adult patients with resting or provoked LVOT obstruction.

As mavacamten has been recently introduced for the treatment of oHCM, data on the real-world use and efficacy of the drug are relatively scarce. In this study we report novel additional observations on the real-world effectiveness of mavacamten, showing that mavacamten reduces even extreme (>100 mmHg) LVOT gradients in oHCM, already after one week of treatment. We also provide data on the efficiency of mavacamten in the reduction of myocardial work, a novel advanced echocardiographic parameter of left ventricular systolic function.

2. Patients and methods

2.1. Patients

A total of twenty-nine oHCM patients were treated with mavacamten. Of these, twenty-five patients [15 men (60 %), mean age: 55 ± 11 years] had a resting or provoked LVOT gradient of >100 mmHg and comprised the study population. Their clinical, demographic, and echocardiographic data are presented in Table 1. The same data for all 29 oHCM patients are presented in Supplementary Table 1.

The investigation conforms with the principles outlined in the Declaration of Helsinki (Br Med J 1964; ii: 177). The study was approved by the Hungarian Medical Research Council (8489–2/2018/EÜIG, 08783–2/2023/EÜIG, 628–1/2018/EKU ETT TUKEB) and the Institutional Research Ethics Committee of the University of Szeged (148/2024-SZTE IKEB). All subjects participating in the study gave prior written informed consent to participate in the study.

2.2. Mavacamten titration

Mavacamten titration was performed according to the instruction for use (IFU) of mavacamten [12], approved by the European Medicines Agency (EMA). Patients were genotyped for CYP2C19 to determine appropriate mavacamten dose. There were two patients with the poor metabolizer phenotypes, the other 23 patients had intermediate, normal, rapid or ultra-rapid metabolizer phenotypes. Starting dose was 2.5 mg in patients with CYP2C19 poor metabolizer phenotype, and 5 mg with CYP2C19 other metabolizer phenotypes. Titration of mavacamten was based on follow-up echocardiographic measurements,

Table 1
Clinical, demographic and echocardiographic characteristics of the hypertrophic cardiomyopathy patient cohort with >100 mmHg LVOT gradient treated with mavacamten ($n = 25$).

CLINICAL AND DEMOGRAPHIC CHARACTERISTICS	
Age, years	
Mean (SD)	55 (11.3)
Median (IQR)	55 (50–61)
Female, n (%)	10 (40)
BMI, mean (SD), kg/m^2	30.0 (4.3)
Genetic testing	
Genetic testing results available, n (%)	20 (80)
Carrier of pathogenic/likely pathogenic (P/LP) variant, n (%)	4 (20)
Identified P/LP variants	*MYBPC3* p.Phe1159TyrfsTer9, *MYBPC3* p.Tyr1136del, *MYBPC3* p.Ser25fs, *MYH7* p.Pro307Ser
Carrier of VUS (variant of unknown significance), n (%)	3 (15)
Identified VUS variants	*DSP* p.Arg1537Cys, *MYL3* p.Pro23His, *DSC2* p.Ala452Val
No variant, n (%)	13 (65)
Baseline NYHA class, n (%)	
Class II	9 (36)
Class III	16 (64)
Duration since HCM diagnosis, mean (SD), years	8 (4.6)
ECHOCARDIOGRAPHIC AND CLINICAL CHARACTERISTICS	
Transthoracic echocardiographic parameters, mean (SD)	
LVEF, %	65.1 (6.0)
Maximal LV wall thickness, mm	24.2 (3.6)
Resting LVOT peak gradient, mmHg	121 (36.1)
Valsalva LVOT peak gradient, mmHg	167 (36.9)
Cardiac rhythm, n (%)	
Sinus rhythm	24 (96)
Comorbidities, n (%)	
Hypertension	18 (72)
Paroxysmal atrial fibrillation	4 (16)
Coronary artery disease	3 (12)
Prior attempted septal reduction therapy, n (%)	
Septal myectomy	0 (0)
Alcohol septal ablation	10 (40)
Background HCM medical therapy prior to mavacamten start, n (%)	
BB monotherapy	5 (20)
Non-dihydropyridine CCB monotherapy	0 (0)
BB and non-dihydropyridine CCB	0 (0)
BB and disopyramide	20 (80)
Prior device therapy, n (%)	
ICD	4 (16)

Data are expressed as mean (standard deviation, SD), median (interquartile range, IQR) or number (percentage). BMI: body mass index, *MYBPC3*: cardiac myosin binding protein C gene, *MYH7*: beta myosin heavy chain 7 gene, *MYL3*: myosin light chain 3 gene, *DSC2*: desmocollin 2 gene, *DSP:* desmoplakin gene, VUS: variant of unknown significance, LVEF: left ventricular ejection fraction, LVOT: left ventricular outflow tract, BB: beta-blocker, CCB: calcium channel blocker, ICD: implantable cardioverter defibrillator.

recommended in the IFU [12]. At W8 visits, all patients were on the 2.5 mg or 5 mg starting doses. In the 7 patients completing W48 visits, 2, 2 and 3 patients received 5 mg, 10 mg and 15 mg mavacamten, respectively. Disopyramide was stopped before initiating mavacamten treatment in all patients.

2.3. Methods

In addition to recording the main demographic, clinical and laboratory parameters, complete standard and 2D-speckle tracking echocardiographic examination was performed in the patients after 1 week (W1) of treatment and in four-week intervals thereafter until 24 weeks and in 12-week intervals until 48 weeks. All patients completed the W8 visit, and 7 patients completed the W48 visit.

Resting blood pressure was measured in the supine position immediately before the echocardiographic examination. All patients underwent comprehensive echocardiography, as well as non-invasive myocardial work analysis. Left ventricular systolic function was assessed comprehensively, including ejection fraction measurement using the biplane Simpson's method. Left ventricular outflow tract (LVOT) gradient was assessed at rest and during the Valsalva manoeuvre to determine peak instantaneous and provoked gradients, respectively. Echocardiographers carefully adjusted the Doppler angle from the left atrium to the LVOT to differentiate mitral regurgitation from LVOT flow. Diastolic function was evaluated according to current guidelines, incorporating tissue velocity imaging (TVI). Left heart speckle-tracking strain analysis included global longitudinal strain (GLS) measurement from apical 2-, 3-, and 4-chamber views. From these data, the following global myocardial work parameters were derived: global work index (GWI), global constructive work (GCW), global wasted work (GWW), and global work efficiency (GWE). Left ventricular peak pressure, used in the GWI, GCW, GWW, and GWE calculations, was determined as previously described [13]. All examinations were carried out with a GE Vivid E95 R4 (GE Healthcare, Horten, Norway) cardiac ultrasound system.

2.4. Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range, IQR) as appropriate. Normality for the distribution of continuous variables was tested by the Kolmogorov–Smirnov or the Shapiro-Wilks test. Temporal change in parameters was assessed by a mixed model repeated measures ANOVA using autoregressive covariance structure. Assumption of normality of residuals was graphically checked, in case of skewed distributions logarithm transformation was used. Pairwise comparisons were performed on estimated marginal means using Sidak correction for multiple comparisons. For categorical variables the Chi-square test and Fisher's exact tests were used. Statistical analysis was done with MedCalc® Statistical Software version 20.106 (MedCalc Software Ltd., Ostend, Belgium; https://www.medcalc.org; 2022). A $p < 0.05$ value was considered as statistically significant.

3. Results

3.1. LVOT gradient of >100 mmHg decreased significantly even after one week of mavacamten treatment

After only one week of mavacamten therapy, the resting peak LVOT gradient decreased by an average of −34 mmHg (95 % CI: −53 to −14), from 121 to 87 mmHg ($p < 0.001$); which decreased further to 56 mmHg at W8 ($p < 0.001$). The LVOT gradient provoked by the Valsalva manoeuvre decreased by −38 mmHg (95 % CI: −60 to −17) at W1, from 167 to 129 mmHg ($p < 0.001$), with a further decrease to 80 mmHg at W8 ($p < 0.001$) (Table 2 and Fig. 1). In the 7 patients completing W48 visits, the resting peak LVOT gradient decreased further to 7 mmHg ($p < 0.001$), and the Valsalva peak LVOT gradient decreased to 9 mmHg ($p < 0.001$).

Table 2
Change in clinical, echocardiographic and biomarker parameters after one week (W1), 4 weeks (W4) and 8 weeks (W8) of mavacamten treatment in oHCM patients with >100 mmHg left ventricular outflow gradient (n = 25).

	Baseline	W1	W4	W8
LVOTG, resting peak (mmHg)	121 ± 9	**87 ± 9*** **	**67 ± 9*** **	**56 ± 9*** **
LVOTG, resting peak, mean difference (mmHg)		**−34 (−53 to − 14)*** **	**−54 (−78 to − 29)*** **	**−64 (−91 to – 37)*** **
LVOTG, Valsalva peak (mmHg)	167 ± 10	**129 ± 10*** **	**102 ± 10*** **	**80 ± 10*** **
LVOTG, Valsalva peak, mean difference (mmHg)		**−38 (−60 to − 17)*** **	**−64 (−91 to − 38)*** **	**−87 (−116 to − 57)*** **
NTproBNP (pg/ml)	2952 ± 602	**1485 ± 604*** **	**1217 ± 604*** **	**904 ± 615*** **
NTproBNP, mean difference (pg/ml)e		**−1467 (−2379 to − 556)*** **	**−1735 (−2951 to − 520)*** **	**−2048 (−3491 to − 606)*** **
Troponin T (ng/l)	35 ± 10	36 ± 10	30 ± 10	**24 ± 10***
6-min walk distance (m)	408 ± 18	**434 ± 18***	**466 ± 18*** **	**462 ± 18*** **
EF (%)	65 ± 1	65 ± 1	63 ± 1	64 ± 1
GLS (%)	−13.7 ± 0.6	−13.6 ± 0.6	−13.5 ± 0.6	−13.5 ± 0.6
GWI (mmHg%)	2098 ± 98	1898 ± 99	**1747 ± 98** **	**1659 ± 101** **
GCW (mmHg%)	2622 ± 112	2404 ± 113	**2206 ± 111** **	**2093 ± 115** **
GWW (mmHg%)	310 ± 25	305 ± 26	278 ± 25	278 ± 26
GWE (mmHg%)	85 ± 1	84 ± 1	86 ± 1	85 ± 1
LAV (ml)	132 ± 5	126 ± 5	119 ± 5	120 ± 5
LAV-index (ml/m^2)	66 ± 2	64 ± 2	61 ± 2	61 ± 2
e' lateral (cm/s)	6.8 ± 0.5	7.2 ± 0.5	7.2 ± 0.5	7.9 ± 0.6
E/e'	18 ± 1	18 ± 1	17 ± 1	14 ± 1
Mitral insufficiency ≥ 3, n/n (%)	15/25 (60 %)	11/25 (44 %)	**4/25 (16 %) ** **	**3/25 (12 %) *** **
Mitral insufficiency ≥ 2, n/n (%)	21/25 (84 %)	17/25 (68 %)	**13/25 (52 %)***	**7/25 (28 %) *** **
LV EDD (mm)	46 ± 0.8	46 ± 0.8	47 ± 0.8	46 ± 0.8
LV ESD (mm)	29 ± 0.9	30 ± 0.9	30 ± 0.9	30 ± 0.9
LV EDV (ml)	106 ± 6	101 ± 6	94 ± 6	101 ± 6
LV EDV-index (ml/m^2)	52 ± 3	51 ± 3	48 ± 3	51 ± 3
LV ESV (ml)	37 ± 2.6	35 ± 2.6	35 ± 2.6	37 ± 2.6
LV ESV-index (ml/m^2)	18 ± 1	17 ± 1	18 ± 1	19 ± 1
IVS (mm)	24 ± 0.7	23 ± 0.7	23 ± 0.7	23 ± 0.7
PW (mm)	13 ± 0.5	13 ± 0.5	13 ± 0.5	13 ± 0.5
Maximal LV wall thickness (mm)	24 ± 0.7	24 ± 0.7	24 ± 0.7	24 ± 0.7

Data are expressed as mean ± SEM or mean (95 % confidence intervals). Values are considered significantly different at $p < 0.05$ (*), $p < 0.01$ (**), $p < 0.001$ (***). Significant changes are highlighted in bold. SEM: standard error of mean, LVOTG: left ventricular outflow tract gradient, EF: ejection fraction, GLS: global longitudinal strain, GWI: global work index, GCW: global constitutive work, GWW: global wasted work, GWE: global work effectiveness, LAV: left atrial volume, LAVI: left atrial volume index, LV: left ventricular, EDD: end-diastolic diameter. EDV: end-diastolic volume, ESD: end-systolic diameter, ESV: end-systolic volume, IVS: interventricular septum, PW: posterior wall.

3.2. Increase of LVOT gradient with mavacamten withdrawal and restoration of gradient decrease with mavacamten re-initiation

A 58-years-old (Patient No. 2.) and a 56-years old (Patient No. 6.) female patient developed atrial fibrillation (AF) after 36 days (Patient No. 2.) and 188 days (Patient No. 6.) of mavacamten initiation. Under mavacamten treatment the LVOT gradient showed a substantial

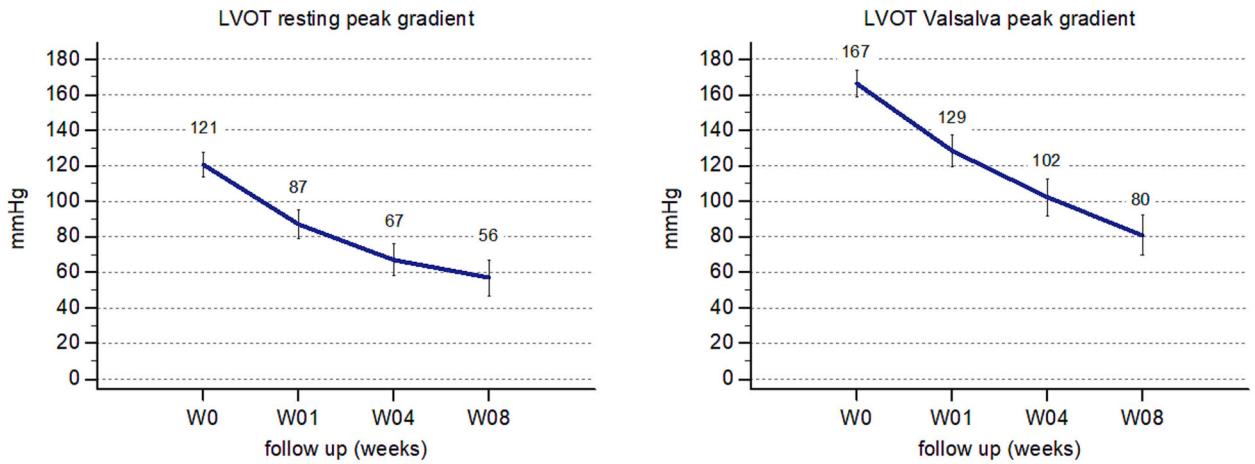

Fig. 1. Change in resting and Valsalva left ventricular outflow tract peak gradients after 1, 4 and 8 weeks of mavacamten treatment.

decrease in both cases (resting LVOT gradient from 100 and 173 to 94 and 76 mmHg at W1, and to 30 and 10 mmHg at the time of mavacamten stop; Valsalva gradient: from 195 and 198 to 132 and 95 mmHg at W1, and to 74 and 25 mmHg at the time of mavacamten stop). A successful electrical cardioversion was performed in both cases with restoration of sinus rhythm. Although LV ejection fraction was not compromised (EF: 62 and 58 %) mavacamten was withhold for precautionary reasons for one month. Without mavacamten therapy the LVOT gradient rose again (resting gradient: from 30 and 10 to 130 and 98 mmHg; Valsalva gradient: from 74 and 25 to 143 and 127 mmHg). After mavacamten re-initiation LVOT gradients fell again rapidly (resting gradient: from 130 and 98 to 12 and 15 mmHg, Valsalva gradient: from 143 and 127 to 25 and 22 mmHg) (see gradient changes in Patient No. 2. in Fig. 2).

3.3. *The decrease in the LVOT gradient was paralleled by a decrease in laboratory biomarker levels*

Parallel to the decrease of the LVOT gradient, NTproBNP levels significantly decreased at W1 by −1467 pg/ml (95 % CI: −2379 to −556), from 2952 to 1485 pg/ml ($p < 0.001$), which further decreased at W8 to 904 pg/ml [mean difference: −2048 pg/ml (95 % CI: −3491 to −606); $p < 0.001$]. In the 7 patients completing W48 visits the mean NTproBNP levels decreased to 269 pg/ml ($p < 0.001$). Changes in troponin T levels were not significant at W1; however, it showed a significant decrease at W8 (from 35 to 24 ng/l; $p = 0.021$). In the 7 patients completing W48 visit the mean troponin T levels decreased to 12 ng/l ($p = 0.021$).

3.4. *Significant improvement in NYHA functional class and 6-min walk distance*

There was no significant change in NYHA functional class observed at week 1. The earliest significant improvement regarding NYHA class occurred at week 4 (W4). At this point, the percentage of patients with NYHA class I increased from 0 % to 8 %, those with NYHA class II increased from 36 % to 64 %, and those with NYHA class III decreased

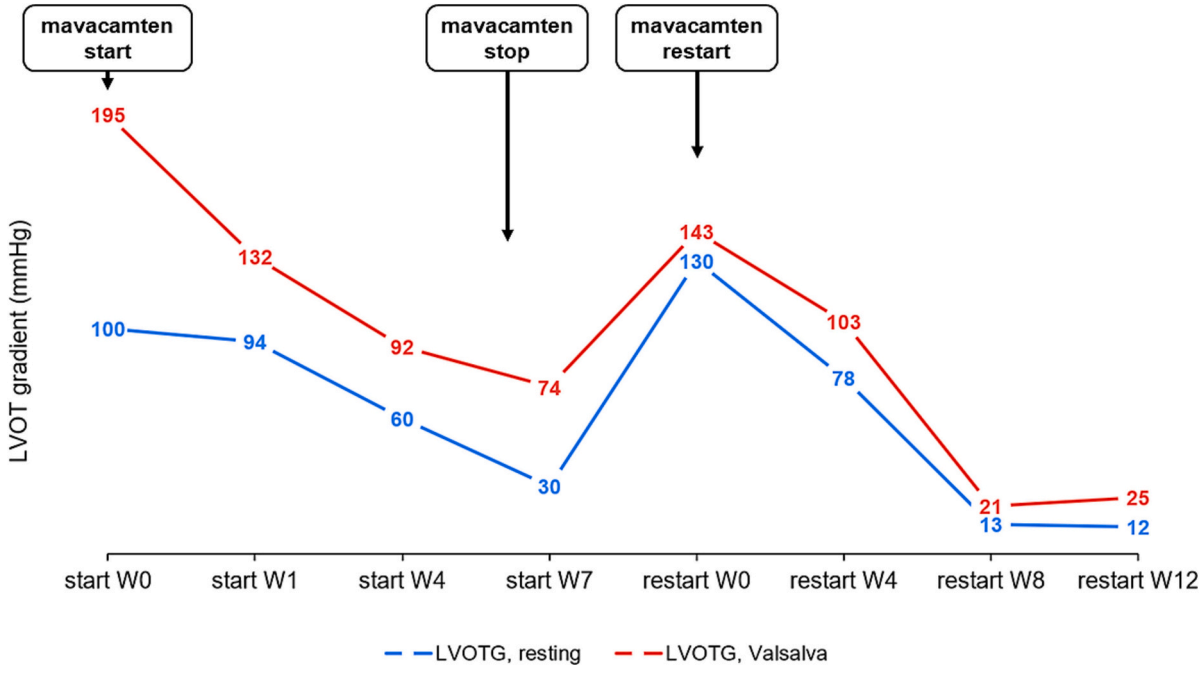

Fig. 2. Increase of LVOT gradient in Patient No. 2. with mavacamten withdrawal and restoration of gradient decrease with mavacamten re-initiation. The start, stop and re-start of mavacamten therapy is marked with arrows. See details in text. LVOT: left ventricular outflow tract.

from 64 % to 28 % ($p = 0.0237$). NYHA class showed further improvement by week 8 (W8), with the percentages of patients in NYHA class I, II, and III being 20 %, 64 %, and 16 % respectively ($p = 0.0008$). At week 48 (W48), 71 % of the patients were in NYHA I, and 29 % of the patients were in NYHA II class.

Parallel to improvement in NYHA functional class, 6-min walk distance significantly improved at the W4 visit [median difference 59 m (95 % CI: 33–85), $p < 0.001$] and remained improved at the W8 visit [median difference 54 m (95 % CI: 23–86), $p < 0.001$] (Table 2). Further improvement was observed in patients completing W48 visits [median difference 92 m (95 % CI: 2–182), $p = 0.043$].

3.5. No significant change of LV diameters, LV volumes, LV ejection fraction or global longitudinal strain

Left ventricular diameters, volumes, ejection fraction and global longitudinal strain did not change significantly neither at W1 nor at W8 visits (Table 2). No further significant decrease was seen in the 7 patients completing W48 visits.

3.6. Despite of no change in global longitudinal strain, myocardial work parameters showed favourable significant changes

As the LVOT gradient decreased, the global work index (GWI) continuously decreased through W8 (2098 vs. 1898 at W1, $p = 0.100$; vs. 1747 at W4, $p = 0.009$; vs. 1659 mmHg% at W8, $p = 0.003$). Global constructive work showed similar changes (GCW: 2622 vs. 2404 at W1, $p = 0.163$; vs. 2206 at W4, $p = 0.009$; vs. 2093 mmHg% at W8, $p = 0.002$). Global wasted work (GWW) and global work efficiency (GWE) didn't show significant changes (GWW: 310 vs. 305 at W1, $p = 0.996$; vs. 278 mmHg% at W8, $p = 0.695$; GWE: 85 vs. 84 % at W1, $p = 0.998$; vs. 85 % at W8, $p = 0.984$) (Table 2).

As values for normal ranges are available for all MW parameters [14], we were able to compare the number of patients with abnormal MW values at the different visits. GWI (normal range: 1292–2505 mmHg %) and GCW (normal range: 1582–2881 mmHg%) was abnormal only in 26 % and 39 % of patients at W0, respectively, which percentage decreased to 9 % regarding both GWI ($p = 0.124$) and GCW ($p = 0.017$) at W8. All patients completing W48 visits had a normal GWI ($p = 0.127$) and GCW ($p = 0.030$). GWW (upper limit of normal: 226 mmHg%) was abnormal in 74 % of patients at W0, which percentage decreased to 48 % at W8 ($p = 0.073$). All patients completing W48 visits had a normal GWW ($p = 0.0009$). Finally, GWE values (lower limit of normal: 91 %) were abnormal in 87 % of the patients at W0, which did not change at W8 (78 %, $p = 0.442$), but was recorded only in 29 % of patients completing W48 visits ($p = 0.003$).

3.7. Favourable changes in the degree of mitral regurgitation, diastolic function and left atrial volumes during mavacamten treatment

The degree of mitral regurgitation (MR) showed significant changes with decrease of ≥3 grade MR from 60 % to 44 % at W1 ($p = 0.297$), to 16 % at W4 ($p = 0.0015$) and to 12 % at W8 ($p = 0.0005$); and decrease of ≥2 grade MR from 84 % to 68 % at W1 ($p = 0.260$), to 52 % at W4 ($p = 0.0164$) and to 28 % at W8 ($p = 0.0001$).

Left atrial volume and volume index values showed a favourable non-significant regression trend through W8 (LAV: 132 vs. 120 ml; $p = 0.175$; LAVI: 66 vs. 61 ml/m^2; $p = 0.492$) (Table 2), the changes were significant in the 7 patients completing W48 visits (mean difference, LAV: −46 ml; $p = 0.001$; LAVI: −23 ml/m^2; $p = 0.001$).

Lateral e' and E/e' displayed non-significant changes through W8 (lateral e': 6.8 vs. 7.9 cm/s, $p = 0.230$; E/e': 18 vs. 14, $p = 0.093$) (Table 2), the changes were significant in the 7 patients completing W48 visits regarding E/e' (mean difference: −7, $p = 0.035$).

3.8. The entire cohort of 29 oHCM patients showed similar changes across all assessed parameters

Across the entire cohort of 29 oHCM patients, the temporal change and the magnitude of changes were similar across individuals for all the assessed clinical, echocardiography, and biomarker changes (Supplementary Table 2).

3.9. Safety profile and adverse events

Three patients developed atrial fibrillation (AF) during mavacamten treatment (a 58-years-old, a 56-years old female, and a 50-years old male), all with a previous history of AF. AF occurred after 36, 188 and 21 days after mavacamten treatment initiation. All patients were converted into sinus rhythm (SR), and remained in SR until last follow up. No hospitalization for heart failure, no major arrhythmia or EF < 50 % occurred.

4. Discussion

As mavacamten has been just recently introduced for the treatment of oHCM, data on the real-world use and real-world efficacy of the drug are relatively scarce. Beyond the two pivotal mavacamten clinical trials, EXPLORER-HCM [4] and VALOR-HCM [5], real world data are available from the long-term extension of the above clinical trials [6,7] and from small, usually single-centre patient cohorts, reporting data on 6–66 patients [15–19] (with the only exception of one report from the Cleveland Clinic reporting data on 150 patients [20]). To expand the real-world data on the clinical use of mavacamten in this work we showed that mavacamten effectively reduced even extreme (>100 mmHg) LVOT gradients and led to significant gradient reduction already in one week. Besides favourable changes in LVOT obstruction, structural and functional echocardiographic parameters, functional capacity, and cardiac biomarkers, it has also led to significant changes in myocardial work parameters.

A novel observation of our study is that mavacamten significantly reduces both resting and provoked LVOT gradients already after one week of treatment. The effect of mavacamten on gradient reduction in clinical trials was assessed at 4 weeks the earliest in both the EXPLORER-HCM [4] and VALOR-HCM [5] trials, and studies reporting real-world data in HCM patient cohorts also assessed gradient reduction only after 4 weeks [15,16]. As mavacamten is readily absorbed with a median t_{max} of 1 h after oral administration with an estimated oral bioavailability of approximately 85 % [12], this relatively rapid action of the drug and rapid onset of clinical response is not surprising. This observation raises the possibility that mavacamten can be used in situations where relatively rapid (i.e., within a couple of weeks) LVOT gradient reduction is needed in oHCM patients.

Another novel finding of our study that mavacamten is also effective in oHCM patients with >100 mmHg LVOT gradients. In the EXPLORER-HCM study the resting and the Valsalva gradient was 52 mmHg and 72 mmHg, respectively [4]; while in the VALOR-HCM study the resting and the Valsalva gradient was 51 mmHg and 75 mmHg, respectively [5]. In the reported real-world oHCM cohorts treated with mavacamten, the resting LVOT gradient was 41–56 mmHg, and the Valsalva gradient was 72–104 mmHg [15,16,20]. In our patient cohort the resting and the Valsalva gradient was 121 mmHg and 167 mmHg, respectively, more than double, than in the clinical trials. Beyond the LVOT gradients the severity of the clinical status of our patient group is also well demonstrated by the increased level of biomarkers. The NTproBNP levels in the EXPLORER-HCM and VALOR-HCM trials were 777 pg/ml and 724 pg/ml, respectively [4,5]; while it was 2952 pg/ml in our patient group. The troponin levels in the EXPLORER-HCM and VALOR-HCM trials were 12.5 ng/l and 14 ng/l, respectively [4,5], while it was 35 ng/l in our patients. As mavacamten treatment was associated with a rapid and significant gradient reduction also in this patient group, according to our

data, the use of mavacamten seems to be equally effective and safe in this very severe group of oHCM patients, like ours.

We were also able to demonstrate that beyond the reduction of gradient, improvement in diastolic function and no change in systolic function, novel echocardiographic measures of myocardial function, parameters of myocardial work (MW), were also reduced rapidly and significantly. As mavacamten directly affects myocardial contractility, the characterisation of change in myocardial work parameters seems to be a primary interest. MW parameters constitute a group of novel parameters which uses pressure-strain loops to estimate myocardial performance [14,21]. MW has been found to be a more sensitive index of segmental and global LV performance compared to EF and GLS. The additive value of detecting MW alteration has been shown for many cardiac diseases including cardiac dyssynchrony, heart failure, cardiomyopathies, coronary artery disease and valvular heart disease [14,21]. The non-invasive estimation of left ventricular systolic peak pressure and therefore the possibility to calculate myocardial work in oHCM has been recently reported [13]. Using this estimation, we observed, that many MW parameters showed favourable changes as the LVOT gradient decreased, with changes in GWI and GCW becoming significant already at W4. As calculation of MW parameters incorporates the estimated LV systolic pressure (which is derived from the systolic aortic pressure and the LVOT pressure gradient) there is a strong correlation between the LVOT gradient and GWI and GCW (but less with GWW and GWE [22]). Therefore, it is not surprising that, with a decrease in the LVOT gradient, GWI and GCW also decrease, which, per se, likely reflects a change in left ventricular pressure due to the gradient reduction rather than a presumed direct effect on contractility. As a consequence, in patients with oHCM, changes in GWI and GCW may not be informative, as these parameters may be in the normal range as GLS is reduced but left ventricular pressure is increased due to the LVOT gradient. However, their favourable change was evident, and abnormal GWI and GCW values returned to normal in all patients. On the other hand, GWW (global wasted work, an index of energy loss) and GWE (global work efficiency) are less correlated with the LVOT gradient [22]. Therefore, their numerical change is not as strongly affected by LVOT gradient reduction as the changes in GWI and GCW. The beneficial changes in GWW and GWE are most clearly demonstrated by the reduction in the proportion of patients exhibiting abnormal values. At baseline, abnormal GWW was present in 74 % of patients and abnormal GWE in 87 %; these proportions continuously decreased throughout mavacamten treatment. In this context, myocardial work parameters may offer additional discriminative power compared to GLS in patients with oHCM, particularly when examining specific aspects of mavacamten treatment, such as response to therapy, treatment failure, or effects in specific patient subgroups (e.g., sarcomeric mutation carriers or patients with pronounced fibrosis). Predicting which patients will develop systolic dysfunction during mavacamten treatment is a particularly important aspect of this issue. However, identifying predictors for this adverse event is challenging due to the relatively low number of patients experiencing LVEF <50 % during mavacamten therapy. Of particular interest, in the VALOR-HCM trial, the mean baseline GLS in the subgroup of 12 patients who required mavacamten interruption was lower than that of the overall study population, with no significant improvement (or worsening) during follow-up. On exploratory logistic regression analysis, a baseline GLS worse than −14.6 % was only weakly associated with the likelihood of developing LVEF <50 %. As myocardial work (MW) parameters may offer additive sensitivity over GLS, their value in predicting the development of systolic dysfunction should be further tested.

As for safety profile and adverse events, patients did not experience hospitalization for heart failure, and no major arrhythmia or EF < 50 % occurred during the observational period. Although an increase in the rate of new onset atrial fibrillation (AF) after the initiation of mavacamten has been reported [23], we had no case with new-onset AF. Three patients (12 %) developed recurrent atrial fibrillation, all with a previous history of AF. This rate is lower or equals to reported AF occurrence rates (both new-onset AF and recurrent AF) after mavacamten initiation which was reported to be 32 % [23], 24 % [24], and 11 % [25] in real-world case series and to be 14 % [6] and 10.2 % [7] in mavacamten long-term extension studies. All of our patients were converted into sinus rhythm (SR), and remained in SR until last follow up.

5. Conclusions

In conclusion, we observed that the direct myosin inhibitor mavacamten effectively reduces even extreme (>100 mmHg) LVOT gradients and has a significant effect even after one week of treatment. Beyond its beneficial effects on structural and functional cardiac parameters it also favourably impacts myocardial work parameters. While long-term results of mavacamten therapy are available from the long-term extension (LTE) studies of the EXPLORER-HCM [6] and VALOR-HCM [7] trials, demonstrating the treatment's long-term efficacy and safety, these promising results derive from the original study populations and are therefore potentially subject to selection bias. Consequently, "real-world" data, preferably from large-scale, multicentre datasets, are greatly needed, with a particular focus on outcome and safety parameters, such as the risk of atrial fibrillation, heart failure, and sudden cardiac death.

6. Study limitations

A clear limitation of our study is the small number of patients in the cohort, particularly the low number of patients completing the week 48 visit. However, our study focused more on the short-term effects of mavacamten treatment. As mavacamten has only recently been introduced for the treatment of oHCM, real-world studies typically report a similar number of patients. The variability and reproducibility of LVOT gradients may pose another challenge; however, the magnitude of changes and the level of significance in the statistical analyses were so high that they are unlikely to be altered in larger patient cohorts. Additionally, 45 % of the study patients had prior unsuccessful attempts at alcohol septal ablation. While the inclusion of these patients with more severe conditions may limit the generalizability of our results, it also provides evidence that mavacamten treatment is effective in this challenging subgroup.

CRediT authorship contribution statement

Viktória Nagy: Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Gergely Rácz:** Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Hedvig Takács:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation. **Krisztina Boda:** Writing – review & editing, Methodology, Formal analysis, Data curation, Conceptualization. **Bianka Polestyuk:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Noémi Schvartz:** Writing – review & editing, Investigation, Formal analysis, Data curation. **László Dániel Vidács:** Writing – review & editing, Project administration, Investigation, Formal analysis, Data curation. **Jenő Antal Pintér:** Writing – review & editing, Visualization, Software, Project administration, Formal analysis, Data curation. **Attila Pálinkás:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Árpád Kormányos:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Tamás Szűcsborus:** Writing – review & editing, Investigation, Formal analysis, Data curation. **János Borbás:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Tamás Szili-Török:** Writing – review & editing, Supervision, Resources, Funding acquisition, Formal analysis, Data curation. **Róbert Sepp:** Writing –

review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Informed consent statement

Informed consent was obtained from all subjects involved in the study.

Institutional review board statement

The investigation conforms with the principles outlined in the Declaration of Helsinki (Br Med J 1964; ii: 177). The study was approved by the Hungarian Medical Research Council (8489–2/2018/EÜIG, 08783–2/2023/EÜIG, 628–1/2018/EKU ETT TUKEB) and the Institutional Research Ethics Committee of the University of Szeged (148/2024-SZTE IKEB).

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Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest in the context of the current study. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

Out of the context of the present study Robert Sepp has participated in advisory boards for and received consulting fees from Bristol Myers Squibb. Viktória Nagy and Hedvig Takács received presentation fees from Bristol Myers Squibb. T.S.-T. received institutional grants from Biotronik, Abbott NL, Biosense Webster, Acutus Medical Inc., Stereotaxis, Catheter Precision, and had consultancy/advisory/speakers contract for product development with Biotronik, Ablacon Inc., Acutus Medical Inc., and Stereotaxis.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2025.133882.

Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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